EFFECT OF THE COMPACTION SPEED ON THE COMPRESSIONAL BEHAVIOUR OF BINARY MIXTURES CONTAINING MICROCRYSTALLINE CELLULOSE AND STARCH

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May 2016

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Työn nimi / Arbetets titel – Title

Effect of the compaction speed on the compressional behaviour of binary mixtures containing microcrystalline cellulose and starch

Oppiaine /Läroämne – Subject

Industrial pharmacy

Työn laji/Arbetets art – Level	Aika/Datum – Month and year	Sivumäärä/ Sidoantal – Number of pages
Master's thesis	May 2016	57

Tiivistelmä/Referat – Abstract

The main goal of this thesis was to examine the effect of the compaction speed on the compressional behaviour of two excipients, microcrystalline cellulose and starch, using an eccentric and rotary presses.

First, the average weights of the tablets have changed due to the increasing speed, as the volume of die kept constant. They were grown, for eccentric press, or were reduced, for rotary press. Second, Compression force, needed to obtain tablets with similar strength, was increased during both tableting methods. The eccentric compaction was more stable regarding to the speed increase. Tablets were formed from all of the blends, with more or less success. Additionally, as a result of force increase, resulted tablets were denser and less porous because of speed expansions during eccentric press. However, the blends containing 80% or more starch were not able to form tablets during the rotary press, because of the very poor die filling. Furthermore, blend containing 60% starch has shown very poor tabletability at speeds over 34 rounds per minute.

The elastic recovery of tablets was very sensitive to the speed rises and to the concentrations of excipients during the eccentric press. Tablets have demonstrated an increase in their elastic recovery values in all cases. However, the tablets with a higher concentrations of starch were significantly more sensitive to the increasing compaction velocity. According to these results, it can be concluded that the starch exhibit more elasticity than microcrystalline cellulose.

The effect of magnesium stearate on tablets' properties, such as the weight and the porosity, and compaction parameters, such as ejection force have also examined. As it expected from boundary lubricants, magnesium stearate has significantly reduced the ejection force values, required for removing the tablet from the die, compared with unlubricated tablets. Additionally, tablets with lubricants were heavier and more porous.

The compression force was adjusted according to the crushing strength values in rotary press. This was due to the fracture variations of such tablets during diametrical compression, which would give unreliable values of tensile strength. Moreover, elastic recovery, porosity, density values were not calculated for scored tablet, due to either the lack of punch displacement data from rotational machine or the relative complexity of measuring the volume of such tablets. If these values had been available for both machines, their comparison with respect to these parameters would be possible and the results of this thesis would have been more appropriate.

Avainsanat – Nyckelord – Keywords

microcrystalline cellulose, starch, compaction speed, compression force, tablet porosity, tablet density, magnesium stearate, eccentric press, rotary press, elastic recovery, ejection force

Säilytyspaikka – Förvaringställe – Where deposited

Library of the division of Pharmaceutical Chemistry and Technology, University of Helsinki

Muita tietoja – Övriga uppgifter – Additional information

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Työn nimi / Arbetets titel – Title

Puristusnopeuden vaikutus binääristen seosten, jotka sisältävät mikrokiteista selluloosa ja tärkkelystä, puristuskäyttäytymiseen

Oppiaine /Läroämne – Subject

Teollisuusfarmasia

Työn laji/Arbetets art – Level	Aika/Datum – Month and year	Sivumäärä/ Sidoantal – Number of pages
Pro gradu tutkielma	Toukokuu 2016	57

Tiivistelmä/Referat – Abstract

Tämän pro gradu tutkielman teoreettisessa osassa on pyritty kattavasti esittelemään farmaseuttisten jauheseosten keskeiset ominaisuudet, kuten myös tärkeimmät tabletoinnin vaiheet. Työssä on pohdittu esimerkiksi puristeen tilavuuden pienenemistä ja sidosten muodostumista samalla kun on esitetty erilaiset puristustekniikat mahdollisimman yksityiskohtaisesti.

Lääkeannosten tasalaatuisuus on eräs keskeinen tekijä, joka kaikkien lääkkeiden tulee täyttää. Tablettien kyseessä ollen tasalaatuisuus sisältää tavallisten kemiallisten ominaisuuksien lisäksi myös monia fysikaalisia tekijöitä, kuten mekaaninen lujuus, dimensiot ja esimerkiksi painonvaihtelu.

Tässä työssä tutkittiin mikrokiteisen selluloosan ja tärkkelyksen sekä niistä valmistettujen seosten puristumista epäkesko- ja rotaatiotablettikoneita käyttäen. Keskeisenä prosessimuuttujana oli puristusnopeus.

Tutkimustulokset osoittivat, että tablettien keskipainot vaihtelivat yllättävällä tavalla puristusnopeuden kasvaessa. Epäkeskokoneella puristettaessa keskipainot kasvoivat ja rotaatiokoneella laskivat. Erityisesti nämä muutokset olivat merkittäviä silloin, kun tärkkelyksen pitoisuus oli suuri.

Tämä voidaan selittää eri tablettikoneiden muodin täyttömekanismilla. Epäkeskokoneella suppilon liike parantaa jauheen valuvuutta suurella nopeudella. Rotaatiokoneella sen sijaan, täyttösuppilo on kiinteässä asemassa ja jauheet valuvat muotiin painovoiman avulla. Näin ollen, lyhyemmän täyttöajan seurauksena tabletit ovat kevyempiä.

Tabletteja pystyttiin valmistaa useimmista seoksista suhteellisen hyvin. Puristusnopeuden kasvaessa, tabletit olivat tiheämpiä ja vähemmän huokoisia, kun pieniä nopeuksia käytettäessä. Jauheista, jotka sisälsivät 80 % tai enemmän tärkkelystä, ei pystytty valmistamaan tabletteja rotaatiokoneella, koska kyseisellä jauheella muoti täyttyi epätasaisesti ja liian hitaasti. Vaikeuksia ilmeni myös tabletoitaessa seosta, joka sisälsi 60 % tärkkelystä, kun tablettikoneen pyörimisnopeus oli suuri (yli 34 kierrosta minuutissa). Tulokset osoittivat, että tärkkelys käyttäytyi puristuksessa elastisesti ja mikrokiteinen selluloosa vastaavasti plastisesti.

Avainsanat – Nyckelord – Keywords

mikrokitenen selluloosa, tärkkelys, puristusvoima, puristusnopeus, vetomurtolujuus, murtolujuus, poistovoima, epäkesko kone, rotaatio kone

Säilytyspaikka – Förvaringställe – Where deposited

Farmaseuttisen kemian ja teknologian osasto

Muita tietoja – Övriga uppgifter – Additional information

Ohjaajat: Jouko Yliruusi ja osmo Antikainen

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1 INTRODUCTION

Tablets are the most widely used drug dosage form in a way that two thirds of all pharmaceutical drug delivery systems consist of tablets (Wu and Seville 2009). Ease of production and dosing as well as improved physical and chemical stability properties comparing with the liquid and semi-solid forms are thought to be the main reasons for their continuous popularity (Jivraj et al. 2000). However, further studies are to be conducted in order to get better understanding of the tableting process, regardless of its easiness comparing with other drug forms.

It is important to understand compaction related terms. In general, powders' process capability is illustrated by tabletability, compressibility and compactability characteristics. The term tabletability symbolizes the relationship between applied pressure and a tensile strength of the resulted tablet i.e. it shows the strength of the compact obtained under the particular force (Sun 2008). The term compressibility is associated with the compression force - porosity profile, illustrating the alteration of tablet porosity under the stress. Compactability can be defined as a correlation between tablet's tensile strength and its porosity – it shows how tablet porosity and tensile strength change under compression.

Tablets must be able to keep their physical, chemical integrity and the dosing uniformity during the manufacture. They also should stay intact after the production until they reach patients. Thus, the mechanical strength is vital feature of tablets (Narang et al. 2010). It must be maintained for successful scale up process. Generally, crushing strength and tensile strength describe the mechanical strength of tablets. According to Fell and Newton (1970) the crushing strength is the force needed to break the tablet under diametrical compression between two flat stiff platens. Tensile strength takes into account the dimensions of tablets, thickness and diameter, along with the crushing strength.

However, mechanical characteristics of compacts may be affected by both formulation-related and compaction factors (Narang et al. 2010). Formulation related problems may occur due to fluctuations in excipient quality attributes, such as particle size distribution, polymorphism, moisture content and shape of particles. Compaction factors, that possibly affect the performance of powder, may include intensity of lubricant mixing, tableting velocity and pressure variations. In addition, environmental effects also have to be considered into account, because the most pharmaceutical excipients are sensitive to the temperature, relative humidity and other similar factors.

In the past, numerous works have been conducted to study a relationship of tablet properties to aforementioned variables. The outcome of these works gives precise insight into this topic. The purpose of this thesis is to examine the effect of compressional speed on mechanical characteristics of tablets. These tablets are made of binary mixture containing various portions of microcrystalline cellulose (MCC) and starch. They were pressed using two type of presses: eccentric and rotary. The mixtures were compacted with a range of speed. Mechanical strength, elastic recovery, porosity and load alterations were analysed. Aims of this experiment are discussed in more detail in the section five.

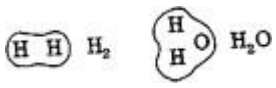
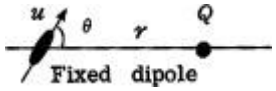
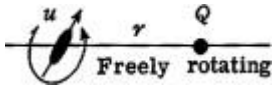
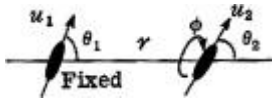
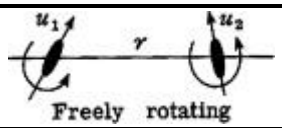
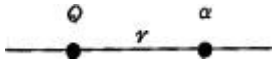
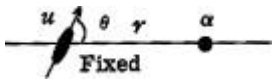
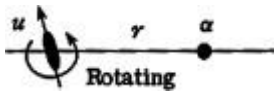
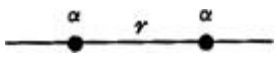
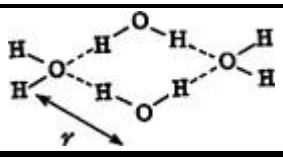
2 INTERPARTICLE INTERACTIONS IN PARTICLE SYSTEMS

Claus Führer (1996) has described powders as “a special case of a dispersed system solid in gas, where the solid particles remain in contact”. Particles in powder bed interact mutually by existing attraction forces between them. As a rule, constant interparticle forces are originated from gravity or other external forces and interparticle attraction forces (Führer 1996). Depending on the nature of interrelating surfaces, interparticle attraction can be divided into adhesive and cohesive forces. If they are of the same sort, it is called adhesive force and if they are of different type, then it is called cohesive force. These forces can also be attractive or repulsive, depending on charge sign. If those charge signs are opposite then forces interact attractively, otherwise they interact repulsively.

According to their chemical and physical origin, forces initiated between particles can be divided into three groups (Israelachvili 2011). The first group include the attractions originated only from electrostatic interaction forces. The interaction occurs because of the result of Coulomb forces between charged particles or because of the interrelation of charged particle and permanent dipole of another particle. Entropic or thermodynamic forces are presented in the second group. It is not correct to describe this group as a direct inter-molecule interaction, because interactions in this group are resulted from their joint behaviour. Third group is very important regarding to pharmaceutical. In this group, there are quantum mechanical attraction forces, which give rise to, for example, van der Waals and charge transfer forces. Van der Waals forces, also known as molecular interactions, are of an electrostatic nature too, although they demonstrate only some degree of electrostatic properties compared to the first group (Führer 1996).

Table 1 shows common types of interactions established between molecules, atoms and ions. It gives also information about free energies of these forces. Only the most important interparticle attraction mechanisms, in terms of pharmaceuticals, are further discussed in more detail.

Table 1. Typical interactions between two atoms, ions or molecules and their energies in vacuum (Israelachvili 2011)

Type of the interaction		Interaction energy w(r)
Covalent, metallic		Complicated, short range
Charge–charge		$+Q_1Q_2/4\pi\varepsilon_0 r$ (Coulomb energy)
Charge–dipole		$-Qu\cos\theta/4\pi\varepsilon_0 r^2$
		$-Q^2u^2/6(4\pi\varepsilon_0)^2kTr^4$
Dipole–dipole		$-u_1u_2[2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos\phi]/4\pi\varepsilon_0 r^3$
		$-u_1^2u_2^2/3(4\pi\varepsilon_0)^2kTr^6$ (Keesom energy)
Charge–non-polar		$-Q^2\alpha/2(4\pi\varepsilon_0)^2r^4$
Dipole–non-polar		$-u^2\alpha\,(1+3\cos^2\theta)/2(4\pi\varepsilon_0)^2r^6$
		$-u^2\alpha/(4\pi\varepsilon_0)^2r^6$ (Debye energy)
Two non-polar molecules		$-\frac{4}{3}\frac{h_p v_a \alpha^2}{(4\pi\varepsilon_0)^2 r^6}$ (London energy)
Hydrogen bond		Complicated, short range, energy roughly proportional to $-1/r^2$

w(r) is the free energy of interaction; *Q*, electric charge; *u*, electric dipole moment; *α*, electric polarizability; *r*, distance between centres of the interacting atoms or molecules; *k*, Boltzmann constant; *T*, absolute temperature; *h*, Planck's constant; *v*, ionization frequency; ε_0, dielectric permittivity of free space;

2.1 Van der Waals interaction forces

Van der Waals interaction forces always exist (Seville et al. 2000). They act between all atoms and molecules, including completely neutral ones (Israelachvili 2011). However, in pharmaceutical development they are considered into account if the distance between interacting particles is very short. Their significance decreases with additional interparticle interval. Furthermore, these forces are not as strong as electrostatic forces (Israelachvili 2011).

As van der Waals interactions consider the attraction forces between permanent and/or induced dipoles of interacting molecules, it is good to understand first the nature of polar molecules. When one atom of the molecule attracts the another one toward itself, it gives to molecule an electric dipole and it becomes polar (Israelachvili 2011). It happens despite this molecule does not have an electric charge. This is called also as a permanent dipole. Induced dipole of nonpolar molecules means a polarization of molecule under electric field of nearby molecules. This field causes displacement of negative electrons to positive ones and molecule will become polarized. Polarization can also be initiated when freely rotating dipolar molecules with zero dipole moment will change their polarity due to the influence of electric filed, which effects the orientations of their rotating dipoles.

Van der Waals forces can be classified into three groups: dipole-dipole, dipole-non-polar (dipole-induced dipole) and the interaction between two non-polar molecules (induced dipole-induced dipole interaction) (Israelachvili, 2011). Dipole-dipole interactions, known also as a Keesom-forces and orientation forces, are the interactive forces between the negative pole of one molecule with the positive pole of another one, when they are in considerably close contact (Israelachvili 2011; Buckton 2007). The equation of Keesom force shows free energy of this attraction (Table 1) (Israelachvili 2011)

Dipole – non-polar or dipole – induced dipole forces consider the relation between permanent dipoles of polar and induced dipoles of non-polar molecules (Israelachvili 2011). These interactions are also referred to as the Debye or induction interaction forces

in the literature. The free energy of these interactions can be described by equation of Debye energy, which is in the Table 1.

The interrelation of two non-polar molecules (London- dispersion forces) characterise the third group. Dispersion forces are the most important contributors to total van der Waals forces (Israelachvili 2011). The reasons for their importance are: their existence between all atoms and molecules and their ability of effecting adhesion, surface tension, physical absorption and the solid's strength. While Keesom and Debye energies are presented or not presented depending on the molecules' properties, London forces are always present. They act over longer distances, comparing with other van der Waals forces, and may be both attractive or repulsive. Moreover, they are non-additive i.e. dispersion force between two molecules is affected by nearby molecules. Furthermore, these forces are considered to be the most important interaction type with respect to pharmaceutics (Adolfsson 1998).

2.2 Electrostatic interaction forces (EIF)

As it mentioned earlier in this study, the basis for the electrostatic interaction forces is given by Coulomb forces resulting from powder manufacturing steps such as production, handling and mixing (Israelachvili 2011). These forces are the result of attraction among relatively highly charged particles and they are active over long distances (Führer 1996). They are also established between charged particle and the permanent dipole of another one (Israelachvili 2011). Additionally, it's impossible to saturate these forces (Führer 1996). The EIF is repulsive if interacting charges are both negative or positive. On the contrary, in the case where the charge signs are opposite, the interaction is an attractive. The equations of energies of these interaction forces are well described in the Table 1.

The triboelectrification is one type of EIF, which occurs due to handling of powders during manufacturing process. The particles collide with each other or with the surface of the instrument because of movement during mixing or other processes (Führer 1996). In turn, these processes make charge transformation between the particles possible. The course of this charge transformation is predicted by the variations in the electron affinity. During mixing or other processes, these collisions continue and every such contact results

interparticle charge transfer, because there is very low possibility that they will find appropriate charged particles for bonding. Because of continuous charge transfer, surface charge densifies further. Homogeneity of the charge distribution on the surface depends on the particle shape. Sphere particles distribute the electrostatic charge more uniformly, whereas with the milled crystals, or other shaped particles with pointed edges, the charge intensity will be greater in the peak of these points.

Polar surfaces are able to form a water sorption layer during storage, because they interact with the water molecules of the environment (Führer 1996). This water sorption layer reduces the surface charge. The rise on triboelectrostatic charge may be exceedingly high for particles with no such layer. It can lead to serious consequences, such as explosions, during operation.

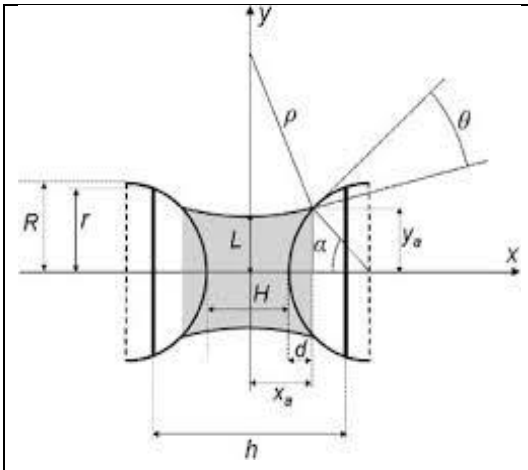
2.3 Water interaction forces (WIF)

The surfaces of polarised materials can adsorb water when placed in moist space, which results the creation of water sorption layer on the surface of particles (Führer 1996). The surface polarity and humidity of the air will determine how thick that water sorption layer will be. The structure of this layer is predicted by the arrangement of the polar groups. Molecules of the water, present on the surface, are connected with each other and with the surface through the hydrogen bonds. Consequently, this sorption layer of water molecules gives to the particles high polarity due to which they can interact with each other with high concentrations of hydrogen bond. This results joint water sorption layer between them.

Separate water phase induces capillary interaction forces. The water phase is present between particles in a wetted powder. It also shows typical liquid characteristics and can form meniscus-shaped bridge in the interparticulate contact regions, if the contact angle between water phase and surface of the particles is small (Figure 1) (Führer 1996). Attraction forces are resulted when the pressure of atmosphere is higher than the pressure of liquid. In the literature, these forces are also known as moisture forces, liquid bridges or capillary forces (Führer 1996; Seville et al. 2000; Megias-Alguacil and Gauckler

2010). They exhibit concrete importance relating to agglomeration processes, inter alia, and demonstrates both dynamic and static forces (Seville et al. 2000). Moreover, they demonstrate either of attractive and repulsive features, though the latter observed in cases where the liquid capacity was small (Megias-Alguacil and Gauckler 2010).

The extent of liquid bridges is adjustable by varying the amount of free liquid between particles, its properties, viscosity and, in particular, surface tension (Seville et al. 2000; Führer 1996). Because pure water gives strong attraction due to its high surface tension.



R is the radius of particles
$\mathbf{x}_\alpha$ and $\mathbf{y}_\alpha$ are the solid-liquid profile contact points
α is an angle of half-filling
θ is moistening angle
ρ and **L** are the radius of the liquid meniscus
H is the interval between the solid particles
d is the wetted area of hemisphere
h is the distance between portions of integration. It used for the calculation of van der Waals force
r the radius of integrated portions

Figure 1. The geometrical illustration of liquid bridge (Megias-Alguacil and Gauckler 2010)

For the calculation of capillary forces, the two parameters should be taken into account: Surface tension of liquid phase and Laplace-Young equation describing pressure difference of the gas-liquid interface (Megias-Alguacil and Gauckler 2010):

$$\boldsymbol{F_{cap} = -2\pi\gamma R \sin\alpha \sin(\alpha+\theta) - \pi\gamma R^2 \sin^2\alpha\left(\frac{1}{L}-\frac{1}{\rho}\right)} \quad \text{(Eq. 1)}$$

Where the wetting and Laplace forces are considered and γ surface tension of the liquid. (For the description other variables in the equation refer to Figure 1). The strength of the capillary forces depends on the shape of the meniscus. It can be defined for any water volume, wetting angle and interparticular distance (Megias-Alguacil and Gauckler 2010).

2.4 Effect of the interparticular interaction forces on powder flow

Particles are in a very close proximity or they even have a direct physical contact among them in powders. Because of these attributes, the force impacting one particle is affected by similar forces active nearby (Führer 1996). Due to very short interparticle distances, interrelation of these nearby forces can be relatively high. Consequently, the powder may not flow, if the force is similar to or higher than particle mass. As die filling happens according to volume of powder in a die, enhanced flow properties are very vital for formulation powders to assure the uniformity of the die filling (Patel et al. 2006).

Any type of interactions, mentioned in the sections from 2.1 to 2.3, may affect the flow of powder bed negatively (Führer 1996). On the contrary, repulsive electrostatic forces may enhance the flow due to decreasing of sticking of particles to each other. As it mentioned in the last paragraph, the die filling happens according to the volume of powder. Thus, bulk density of mixtures must be homogenous during compaction. On the contrary, the rapid changes of electrostatic forces', especially triboelectrostatic forces', charge and inhomogeneous occurrence within the formulation mixture may affect the bulk density of formulation.

Generally, the complete elimination of these attractions from the powder butch is unmanageable; there are many ways to decrease their negative impact (Führer 1996). Keeping of powder bed in the environment, where the relative humidity is about 70 %, may reduce the intensity of all electrostatic forces. Free water molecules in the air causes water sorption layer. The water sorption layer improves surface polarity. It should be noted that only surfaces of polar materials can produce water sorption layer. Non-polar materials can be polarized by treating them with excipients such as Aerosil. Additionally, treatment of the mixture with ionised air or humid air, in cases where materials are not sensitive to humidity, is employable. Furthermore, the addition of amphiphilic excipient or isolation of charged regions on the surface with Aerosil may assist the decreasing of interparticle attraction forces.

2.5 Segregation

In the case of perfect mixture, although it is practically impossible to have it, the proportion of each particle in the sample taken from any position of that mixture will be the same as in the whole mixture (Rhodes 2008). Thus, obtaining of random mixture is targeted generally, as it could probably hold all kinds of particles in all regions of the mixture with the equal concentrations as in the whole system. Random mixture is producible by mixing particles with a similar physical property, as they are not tending to segregate (Rhodes 2008). In the reality, however, particles presented in the powder blend may vary by size, density and shape. This makes occurring of segregation phenomenon possible (Hogg 2009). Additionally, particle properties, like elasticity and surface roughness as well as interparticle attraction forces, may also induce it (Mosby et al. 1996). According to Hogg (2009), these variations in particle properties give rise to differences to their mobility, which in turn trigger the segregation.

Segregation is the separation of similar particles into different zones according to their physical characteristics (Mosby et al. 1996). Separation according particle size takes place simply by better permeability of smaller particles in the powder bed during vibration or flow of powder (Hogg 2009). Segregation of different shaped particles occur only if that difference is considerable e.g. spheres particles mixed with the needle-shaped ones. Although the density variations may cause the segregation as well, it is not as significant as e.g. effect of particle size variety. Interparticular interaction forces may initiate the segregation if they are strong and are long-range acting.

3 TABLETING

3.1 Bond formation and volume reduction mechanisms

Tablet can be described as an air phase spread in a continuous solid phase or, vice versa, solid particles that are spread in a continuous air phase (Nyström et al. 1993). It is formed as a result of compaction process, which is the most critical stage of tablet manufacture (Patel et al. 2006). The strength, physical characteristics, bioavailability and integrity of final compact are dependent from this step. When the load applied on a powder bed inside the die, first particles fill the available voids between them and change their positions (Johansson 1999). This rearrangement of particles is the most significant part of the primary volume reduction of powder bed (Patel et al. 2006). Considering that there is no further space is available for repositioning, they start to deform or fragment with additional compressional load (Adolfsson 1998). Under the stress materials can exhibit elastic and plastic deformation for ductile materials or fragmentation for brittle materials or demonstrates combination mechanism of deformation (Jain 1999). However, most pharmaceutical ingredients display mixed mechanism of consolidation, where each volume reduction types exist in some degree (Ruegger and Çelick 2000). As a result, it is impossible to classify them according to the dominant type of deformation.

Elastic behaviour is the reversible process i.e. material can resume its initial volume when load is removed. Whereas the plastic deformation is irreversible process where it deforms permanently (Patel et al. 2006). Additionally, during fragmentation brittle materials break into smaller particles resulting the increase of contact points.

Bond formation between particles, when compacted, is the precondition for producing robust tablet with defined mechanical strength (Johansson 1999). Because of volume reduction, the molecules or particles are brought to a very close proximity (Adolfsson 1998; Patel et al. 2006). This causes formation of bonds between them. The known bonding mechanisms between materials, according to Rumpf (Alderborn 2007), are the interparticle forces, solid bridges, mechanical interlocking, bonding due to capillary and

tension surface forces and binder bridges for granules. From these interparticle forces, including van der Waals, hydrogen and electrostatic forces, and solid bridges are the most significant types in tablet formation. A mechanical interlocking presents some importance for certain materials consisting from atypically shaped particles. On the contrary, London dispersion forces, one subtype of van der Waals forces, are believed to be the most essential type of bond formation regarding to direct compression (Adolfsson 1998; Alderborn 2007).

The formation of solid bridges take place when two particles will unite their interface or diffuse forming new continuous solid matter (Alderborn 2007). This process requires increasing mobility of particles for being able to mix their boundaries (Führer 1996). The mixing of boundaries can be facilitated by melting under the heat, present during manufacture, or dissolving due to water sorption layer, present on the surface of solids. Internal potency of particles will determine the entire strength of solid bridges. Although the fracture of solid bridge achievable, resulting particles will differ from original ones. That means this phenomenon is irreversible i.e. it is impossible to get original particles by any means.

Mechanical interlocking is the twisting or hooking of particles to each other under the compaction load, when their shape is out of the ordinary e.g. needle shaped (Nyström and Karehill 1996). It is also possible that already formed bonds of this character may again rupture due to excess compaction forces mainly by slipping of contact points (Adolfsson 1998).

Hydrogen bonds can be classified as a bonding of the atom of hydrogen with a donor and an acceptor electronegative atoms (Dingley et al. 2001). The positive charge funded by donor – hydrogen connection and the negative charge is promoted by acceptor atom. However, there is an opinion that suggests, there are two requirements for naming this attraction as a hydrogen bond – first is that the bonding established locally and the second is that the D – H link is able to be as a proton donor to acceptor atom A (Steiner 2002). This connection of the three can be illustrated as D – H----A, the donor is presented by D – H group and acceptor by A. Hydrogen bond, in principle, is a combination of many

interaction forces. The interaction forces, which contribute to hydrogen bond the most, are: electrostatic, dispersion and covalent interaction forces. Thus, its total energy depends on portions of these interaction forces. Electrostatic term is the largest contributor to H-bond strength and is particularly significant in terms of long interparticle distances for its activeness over long intervals. Similarly, van der Waals attractions are the most important for the weakest H-bonds.

3.2 Direct compression (DC)

Direct compression is the easiest way of tableting, where formulation is first mixed and then compacted (Patel et al. 2006). It excludes relatively challenging steps like granulation or agglomeration (Thoorens et al. 2014). Advantages of direct compression are low cost, minimum steps involved in the process, faster dissolution of drug agent into primary particles and improved stability of drug due to e.g. excluding the moist and heat (Alderborn 2007). However, there are certain requirements for DC powders such as displaying great flowability and less segregation properties in addition to superior compactability (Patel et al. 2006). Generally, specially designed excipients are expensive and they should be analysed more thoroughly prior to compaction thus putting the cost-effectiveness of this process under question (Alderborn 2007). Moreover, as it is preferable to use large-sized particles in direct compression, mixing the powder would be challenging, hence causing the segregation. Furthermore, it is mainly employed for the compaction of large-size particle soluble drugs and for drugs, which has very low concentration in the formulation.

3.3 Tableting equipment

In the field of pharmacy, eccentric or single-punch and rotary presses are employed generally (Alderborn 2007). The main difference between them is that eccentric tablet machine uses one pair of punches and only upper punch moves downward to apply the load. Whereas, in rotary press the number of punches may reach 60 or even more and the compression force is applied using both upper and lower punches. The tableting velocities

are maximum 200 tablets per minute for eccentric press and more than 10000 tablets per minute for rotary press. Additionally, employing environment of these two varies: former used mostly during the preformulation or for manufacturing of clinical trial butches and the latter is applied for high-speed industrial production or for the production of tablets for the later phase trials.

3.3.1 Rotational press

In rotary press number of punches fixed in circle on the die table and they operate with the same number of punch pairs by rotating together (Alderborn 2007). Contrary to single-punch press, here the hopper is stationary and powder flows directly onto the feed frame which apply the powder into the die evenly. Upper and lower punches move through the pathway where cams and rolls control the volume of powder in the die and load application (Figure 2). The process can be divided roughly into four stages: die filling, adjustment of powder volume in the die, actual compaction process and ejection of tablet from the machine (Figure 2). The blend is applied into the die by feed frame, where it has been flown due gravity from the hopper. The filled die moves forwards to volume control area where excess powder is removed from the die. Then starts the compression stage that may include pre-compression, main compression, decompression steps and ejection of tablet from the die (Patel et al. 2006). During pre-compression usually smaller force applied to the powder bed by smaller rolls. Regarding to brittle materials, if pre-compression is higher than main compression, it may result stronger tablets. On the contrary, plastic materials require gradual force application for minimising e.g. elastic recovery and form tighter bonds. In the main compression step, larger rolls apply high compaction load. In this step, the primary volume reduction occurs until all interparticle voids are filled by repositioning of particles. After that, particles start to deform or to fragment. The excess force, applied at the end of deformation and fragmentation, mainly contributes to forming interparticulate bond formation. In the next stage, compression force is removed and elastic recovery of material occur causing new stress on material. This stage is named as decompression. To preserve the tablet integrity formed bonds must be stronger than forces caused by elastic recovery. Otherwise, compact may fail.

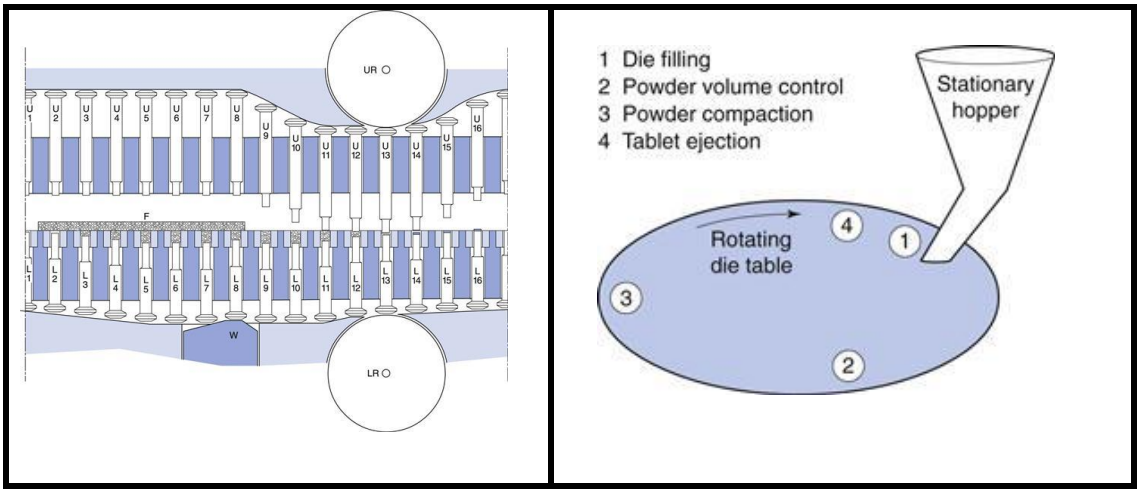


Figure 2. The structure and process steps of rotary press (Alderborn 2007)

The last step of compression is the ejection of compact from the die (Alderborn 2007). It requires force to overcome the radial forces, share forces, adhesion of compact to the die wall and other attraction acting in the die. After an ejection, feed frame pushes tablet away from the tableting instrument.

3.3.2 Eccentric press

The main elements of eccentric tableting machine are the hopper shoe, where the compacting mixture is held, the die, upper and lower punches, capacity and ejection adjustment screws (Figure 3). As it mentioned earlier in this work, hopper shoe here is not stationary i.e. it moves forward and back on the die table. The die is filled when the hopper shoe is located over it by gravitational flow of powder (Alderborn 2007). Hopper shoe then moves back to its original position and upper punch moves downward into the die to apply compression load. The lower punch is in its fixed position i.e. it does not move during compression. After applying the force, upper punch returns back to its initial position by moving upwards. The tablet in the die is ejected through upward movement of lower punch and subsequently forced out of machine by hopper shoe moving for the next die filling.

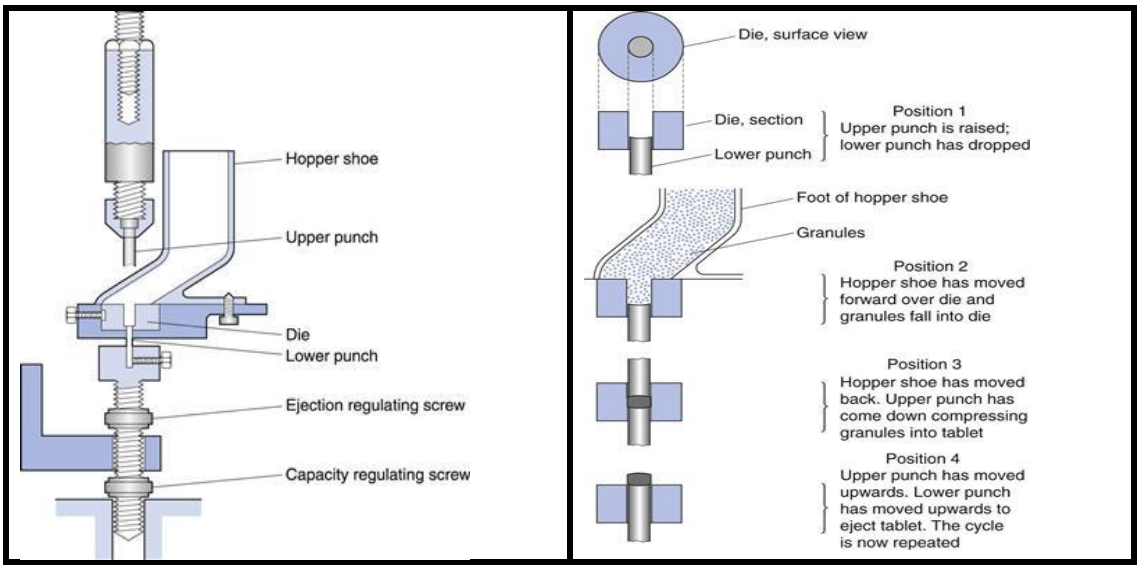


Figure 3. The structure and the scheme of operation steps of single-punch press (Alderborn 2007)

4 FACTORS AFFECTING MECHANICAL STRENGTH OF TABLETS

4.1 Material variables

Along with the active pharmaceutical ingredients (API), excipients are used in the production of tablets. The reasons for their addition to the formulation can be increasing the bulk volume of API, facilitating the parameters of compaction process and adjustment of tablet's biopharmaceutical characteristics (Sinka et al. 2009). They have a lot more functions in the formulation, which is widely described in the literature.

Following requirements generally demanded from the all excipients used in pharmacy (Jivraj et al. 2000). First, excipient should remain physicochemical stability when contacted with external factors, such as heat, moisture and air. Second, chemically neutral, meaning that it should not react with drug agent and other excipients, which can result the degradation of tablets. Third, well suited with the material used for packaging and fourth, offered globally and available from several suppliers.

The proportion of excipients in drug formulation may reach until 99% and, as a result, they can have a considerable influence on the compressional behaviour of formulation mixtures (Dave et al. 2015). The sources of excipients may vary from plants to animals and they are used for any type of drug form and administrating routes. Excipients are generally produced in a large quantities and the batch-to-batch variation or even differences between containers is possible (Thoorens et al. 2014). Additionally, seasonal variation of excipients of natural background and deviations of processes used by each manufacturer should be considered. It is almost impossible to have excipients with constant quality. Therefore, it is very important to thoroughly understand the impact of these variations in quality on compressional behaviour of these excipients and subsequently, on the characteristics of final compacts.

4.1.1 Polymorphism

Generally, pharmaceutical powders consist of different polymorphs of the same material (Buckton 2007). Polymorphs differ from each other with the packing order of molecules in crystals. Typically, polymorphism caused by alterations of circumstances of the crystallization. For instance, by instabilities during cooling period, solvent variations or various impurities. Therefore, the densities of polymorphs may vary together with their dissolution properties and bioavailability.

Polymorphism affects the compressibility of pharmaceutical powders too. In general, the most thermodynamically stable polymorphs form weaker tablets than the less stable ones (Sinka et al. 2009). Figure 4 illustrates this phenomenon.

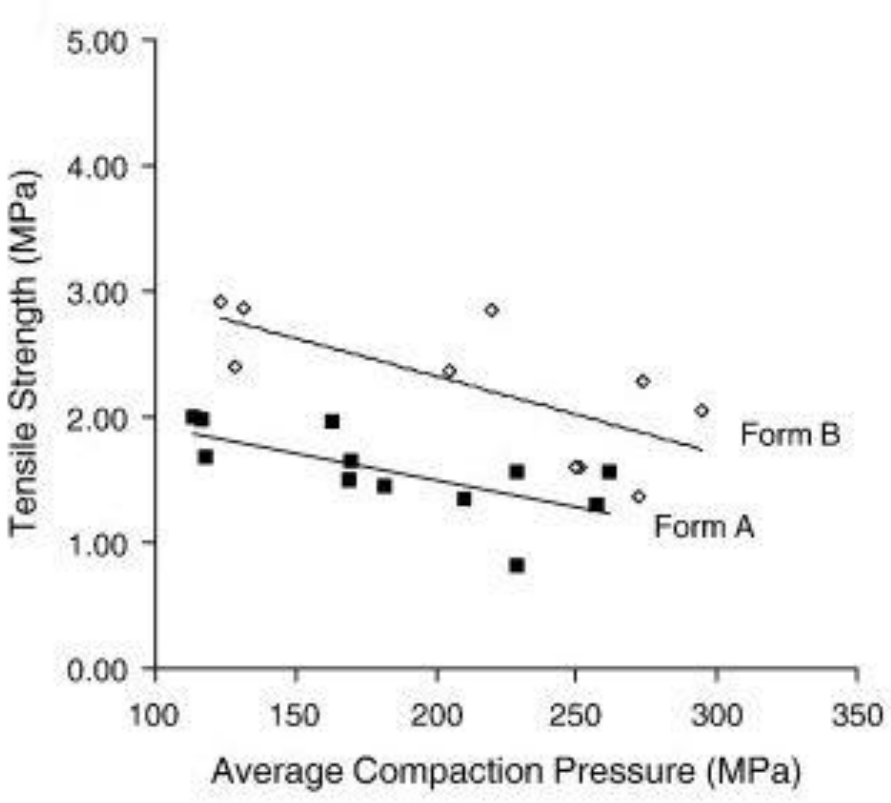


Figure 4. Compaction behaviour of different polymorphs. A – More stable form; B – less stable form (Sinka et al. 2009)

4.1.2 Moisture content

One more factor that has an effect on the performance of the formulation blend is its moisture content (Nokhodchi et al. 1996 a). It has a substantial importance because of its influence on deformation tendency of materials. Nokhodchi et al. (1996 a) have examined the effect of an existent moisture on the compaction behaviour of hydroxypropylmethylcellulose 2208. They found that, for a given load the increase in wetness of this material escalates the relative density and reduces resistance to deformation. Similar result was displayed during another study, where the additional water has risen the density of the powder, probably, due to antiplasticization effect (Sun 2008). Higher moisture content has also decreased the amount of plastic energy needed for producing compact with particular tensile strength (Nokhodchi et al. 1996 a). Moisture content can improve the flow properties of powders as well, due to the decrease of the electrostatic attractions between particles (Nyqvist and Brodin 1982). In contrast, increase in moisture content of MCC has caused fall in flowability (Amidon Houghton 1995). Amidon and Houghton (1995) have also shown that the tensile strength of microcrystalline cellulose, is relatively less sensitive to the moisture until 5%, but affected when it has grown above this limit. This agrees with the results of different research, where MCC with more than 5% water displayed fall in its strength, although harder compacts were obtained with increasing moisture until that limit (Sun 2008). Based on the results of this work, the ideal moisture content for MCC was proposed to be from 3.3% to 5%.

4.1.3 Particle size and shape

Particle size and shape of the material also play very important role during compaction. Variations in the size of particles can modify the consolidating mechanism of a material (Ishino et al. 1990). They also effect tensile strength, elastic (plastic) energies and the elastic recovery of compacts (Nokhodchi et al. 1995).

The effect of the particle size on compression parameters of pure paracetamol powder was successfully shown by Garekani et al. (2001). They have investigated two size fractions of paracetamol, which consolidate by fragmentation under pressure. The results have indicated that paracetamol powder with larger size particles produced denser tablets due to broader fragmentation. Tablets resulted from this fraction were also less prone to elastic recovery and showed lower elastic energies compared to tablets made of powder containing smaller size fraction.

The shape of particles also plays considerable role in determining the strength of bonds, as the surface area of particles is strictly connected with their shape (Abdel-Hamid et al. 2011). Because of its relation to the potency of interparticulate bonds, available surface area is one factor determining the mechanical strength of tablets (Adolfsson 1998). Tablets get fractured along the particles, not through them i.e. longer interparticulate contact areas require more force for fracture. Furthermore, small and irregularly shaped particles exhibit more plasticity during high speeds than bigger and smoother ones (Abdel-Hamid et al. 2011). Results of some researches indicate that, the effect of the particle shape is only considerable with plastic materials and brittle ones are independent of this feature (Alderborn and Nyström 1982).

4.2 Process variables

4.2.1 Interrelation of mechanical strength and characteristics of mixing procedure

One of the important processes in tablet production is a blending process. Sometimes, it effects many other processes such as powder flow, behaviour under compression as well as the mechanical properties of resulted tablets. Quality of blending process is impacted by some factors resulted from the earlier processes such as granulation and drying (Suzuki et al. 2015). In tablet formulation, there are different types of mixers used typically. According to their environment type, blenders can be divided roughly into two groups: laboratory and production scale blenders. In preformulation, not much of sample powder is available and because of this, usually smaller mixers are utilized. On the other hand,

volumes of handling powder blends are much bigger in industrial level. Their devices handle higher load and higher volume.

In terms of lubricant mixing, the effect of blender type, volume, filling load, mixing time, mixing speed on mechanical properties and dissolution features of compact have successfully shown by many researchers (Bolhuis et al. 1987; Kushner IV and More 2010; Chowhan and Chi 1986). Results of these works demonstrate strong evidence that all of these aspects can significantly affect the crushing and tensile strength of final compacts. Additionally, they have affected tablets' disintegration time.

Bolhuis et al. (1987) have described the relation of hardness and lubricant mixing characteristics very well. They have used wide range of blenders from laboratory to industrial level with varying blending techniques (Table 2).

Table 2. Effect of the mixer type, volume and speed on mechanical strength of tablets in terms of crushing strength of the test formulation (Bolhuis et al. 1987)

Mixer and capacity		Rotation speed	Crushing strength half-life	Critical mixing time
Turbula	2 L	45 rpm 90 rpm	1.0 min <1.0 min	10.5 min 1.5 min
Cubic	13 L	20 rpm 60 rpm	8.0 min 2.7 min	30.0 min 17.0 min
Drum	45 L	10 rpm	1.0 min	9.0 min
Planetary	90 L	25 rpm 42 rpm	1.0 min <1.0 min	4.0 min 2.0 min
Planetary	200 L	26 rpm	2.0 min	3.8 min
Planetary	900 L	10 rpm	3.3 min	7.9 min
V-shaped	1000 L	22 rpm	1.5 min	3.6 min

Crushing strength half-life and critical mixing time in the table are the time needed to halve the initial crushing strength and a period in which crushing strength decreases below acceptable limit respectively. Their finding suggest that this relation is more significant in high volume blenders. The lubricant distribution and decrease in hardness was faster

in an industry equipment due to the stronger shear forces present in these blenders. These forces cause of higher pressure on particles.

Kushner IV and Moore (2010) have investigated the effect of the blender type, load and speed of mixing on the tensile strength of tablets. V-type, Bin and Turbula blenders with volumes ranging from 0.75 L to 200 L, load variety was between 30% -70%, speed range from 6 rpm to 202 rpm and mixing time up to 225 minutes were used. Results have clearly demonstrated that, by adding both lubricant mixing time and speed, the tablet hardness decreased in all types of blenders. It is noticeable that slower and longer mixing has shown similar results with faster and shorter mixing. They have investigated the effect of the mixer size and load on the tablet hardness too (Figure 5).

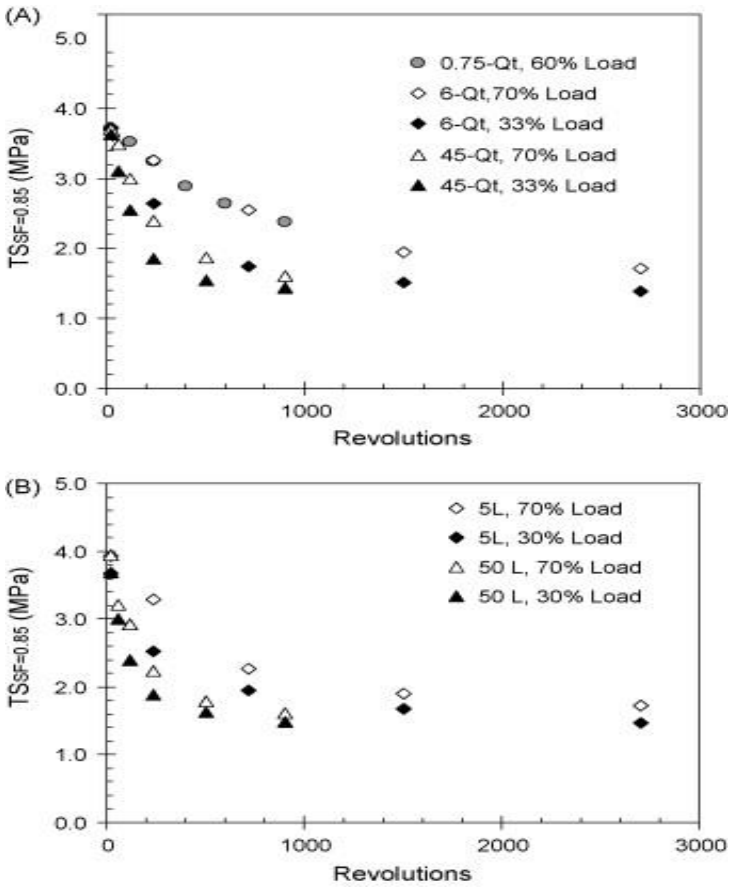


Figure 5. The tensile strength of tablets, at solid fraction of 0.85, as a function of the number of revolutions of mixers, with various volume and load. A- V-blenders, B- Bin Blenders (Kushner IV and Moore 2010)

Results showed that, when filling load and number of blender revolutions was same, the tablets resulted from the blends mixed using smaller blenders were harder than tablets made of mixtures blended in greater devices. However, fall in tensile strength was observable in all cases during addition of mixer velocity. Lower filling load also showed to decrease the hardness of resulting tablets comparing to higher filling.

Ragnarsson et al. (1979) have investigated the role of lubricant mixing time and the concentration of the lubricant in terms of tensile strength, porosity and disintegration time of tablets. They have demonstrated that both the concentration and mixing time had influence on tablet strength and dissolution properties of compacts. Short lubricant mixing time reduced that negative impact without affecting the lubricant efficiency of magnesium stearate. Adding lubricant to all mixtures have also reduced the porosity. Scientists have recommended mixing powders with magnesium stearate during shortest possible time and in lower mixing intensity.

4.2.2 Impact of compaction speed on the mechanical potency of tablets

Nowadays high-speed rotary tablet machines are entirely employed in the manufacturing of tablets in a production scale (Ishino et al. 1990). Even though no problems were observed during trial compactions in the preformulation stage employing single station instrument, unpredicted problems, such as capping and lamination, may occur in a scale-up procedure from laboratory to industry level. (Ruegger and Çelick 2000). It is believed that the rise in the velocity of compaction might be the main reason for causing such trouble during this transformation. However, not all materials are affected by increasing tableting velocity. It is believed to be dependent on consolidation mechanism of materials to be compressed and the particle size distribution of these materials (Ishino et al. 1990; Tye et al. 2005).

As it mentioned earlier in this study, when pressure is applied materials consolidate exhibiting viscoelastic, elastic, plastic deformation or express fragmentation of particles to smaller ones. Plastic and viscoelastic deformations are believed to be time dependent due to the tighter bond formation resulting from prolonged applying of load (Ruegger and

Çelick 2000; Ishino et al. 1990). Additionally, the time dependency of such materials connected with their stress relaxation after compaction, which is the characteristics of ductile materials (Tye et al. 2005). Moreover, materials displaying plasticity are more prone to capping, lamination and strength reduction problems relating to an increase in tableting speed (Ruegger and Çelick 2000). Brittle materials express less sensitivity to the compaction speed and this is because of the quick fragmentation of particles, that is making duration of dwell time insignificant (Tye et al. 2005; Ruegger and Çelick 2000). Furthermore, increasing compaction rate will not alter yield pressure of brittle materials, though the yield pressure of plastic substances increases due to the rise in compression speed (Ruegger and Çelick 2000). Two differently deforming materials can also affect the main deformation mechanism of each other in binary mixtures. Guo et al. (1999) have successfully demonstrated this trend by showing the tendency of riboflavin sodium phosphate, mainly fragmenting material, acting plastically when mixed with MCC, which is known as a ductile material. Tendency of change of the aspirin's deformation behaviour, because of the consolidating nature of co-existing excipient, has been demonstrated during another experiment (Cook and Summers 1990).

Ishino et al. (1990) have examined the effect of compression speed on compactability and compressibility of two widely used directly compressible excipients, MCC and lactose, with varying particle sizes under high speed compression. As it can be expected from brittle materials, effect of tableting speed was insignificant independently from the sizes of particles relating to lactose. The strength of MCC tablets, however, was affected by compression rate variety, although this dependency was smaller when particle size of MCC powder was reduced. The reason for this phenomenon might be an alteration of the main deformation mechanism with changes in particle sizes (Roberts and Rowe 1987). It is also interesting to observe that the tablets resulted from the powder containing smaller particles showed higher tensile strength than those of larger particle fraction, even though the porosity of the two was the same (Ishino et al. 1990). Possible explanation of this tendency is the ability of smaller particles packing more efficiently (Tye et al. 2005).

The results of some studies have shown slightly differing interrelations between consolidation behaviour of materials and sensitivity to dwell time changes. Tye et al.

(2005) have analysed dependency of tablets' strength, produced from the four popular excipients: MCC, DCPD, lactose and pre-gelatinised starch, on tableting velocity. Placebo mixture containing 64.5 % Lac and 35.5 % MCC has also been tested. Figure 6A shows the tabletability of those excipients at constant dwell time. With the lactose, which expresses, mainly, fragmenting behaviour and only some plasticity, the strength of resulting tablets was unaffected by the reduction of dwell time (Figure 6B). Dibasic calcium phosphate dehydrate can be expected to demonstrate similar outcomes with lactose, as it is the very typical brittle material. Surprisingly, the tensile strength of tablet formed from this substance has enhanced with additional punch velocity (Figure 6D). Researchers have explained this trend by the broader fragmentation of particles of DCPD with speed enhancement. The similar occurrence has also been demonstrated by an alternative work, where the aspirin compressed with variety of excipients displayed enhancement of tensile strength at higher speeds (Cook and Summers 1990). In contrast, starch was very sensitive to speed boost due to its plasticity and the mechanical potency of starch tablets was considerably affected by the compaction speed (Figure 6C) (Tye et al. 2005).

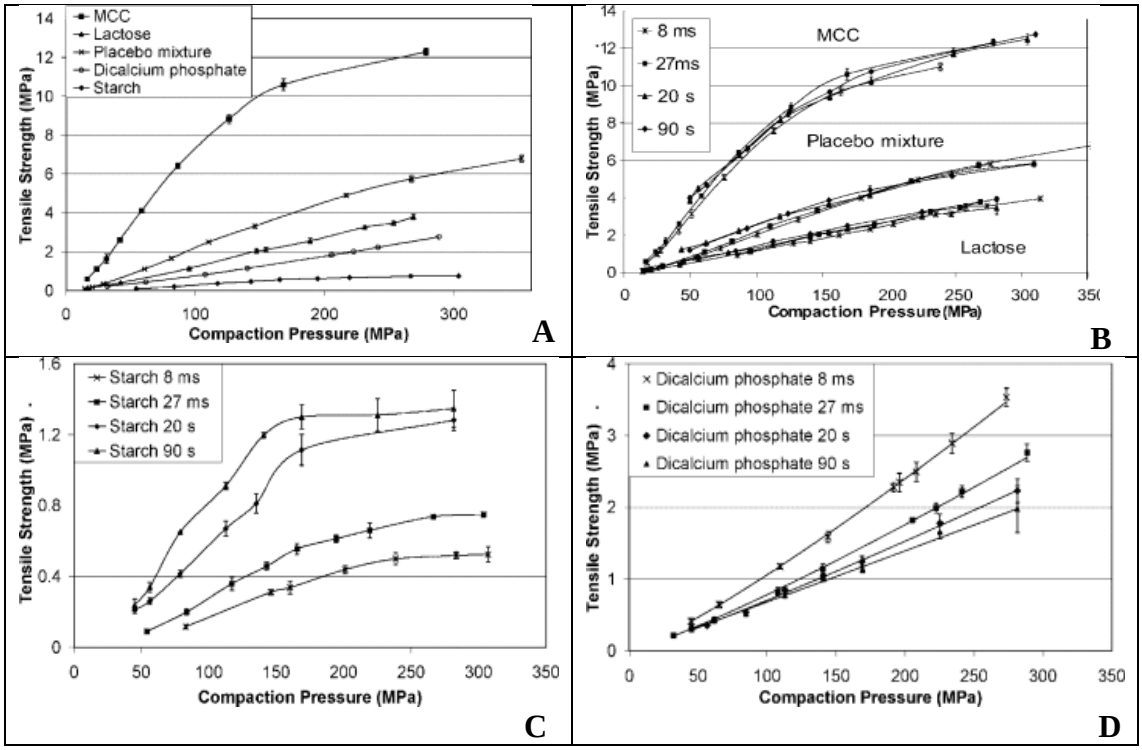


Figure 6. Tabletability profile of four materials in varying dwell times. A: Dwell time is 27 ms. (Tye el al. 2005)

Variations in tensile strength of tablets, compressed from different viscosity grades of the hydroxypropylmethylcellulose, as a result of additional punch velocity have also been investigated (Nokhodchi et al. 1996 b). For HPMC, known for its plasticity, the rising of tableting speed has considerably weakened tablets. Sensitivity of different viscosity grades of HPMC to these changes was dissimilar and their performance differed slightly in terms of speeding up the compaction.

Some researchers have suggested to deal with a loading and unloading speeds separately (Ruegger and Çelick, 2000). The reason for that is the adjustment of compressibility of powders during speed variations can be managed more appropriately by considering loading and unloading speeds as a separate phase.

4.2.3 Impact of compaction force on the mechanical potency of tablets

The extension of applied load on mixtures generally increases the hardness of resulting tablets (Tye et al. 2005; Sinka et al. 2009). This increment will level off at some point due to porosity reduction to levels close to zero, which means there is no additional space for further volume reduction (Adolfsson and Nyström 1996). The continuous increase of compression force after that limit will result in the transformation of the extra compression energy to elastic energy (Adolfsson 1998). In this case, two factors will support elastic recovery: the rupture of formed interparticle bonds and the enlargement of particle into their original sizes (Adolfsson and Nyström 1996). Elastic recovery is also believed to be one of the main causes of capping and lamination occurrences, which results in decreasing the tensile strength of compact.

On the other hand, the additional load may affect the solid state of compacting material, depending on the nature of the material itself (Adolfsson and Nyström 1996; Adolfsson 1998). Such effects vary depending on the solid properties of different materials such as melting point. Excipients with lower melting points show more sensitivity to the high load and during the expansion of applying force, and their degree of crystallinity increases during the expansion of applied force. Whereas materials with higher melting point may demonstrate fall in crystallinity.

Nokhodchi et al. (1996 b) have investigated the influence of compression force and speed on tablets compaction properties, where they noticed that the rise in compaction force has added the tensile strength of compacts made of all four viscosity grades of hydroxypropylmethylcellulose (HPMC) (Figure 7). The effect of applied force over different grades of HPMC showed slight variation. In this work, the researchers have also demonstrated that the tablet porosity was very sensitive to compressional force and it was the porosity, which controlled the tensile strength of tablets.

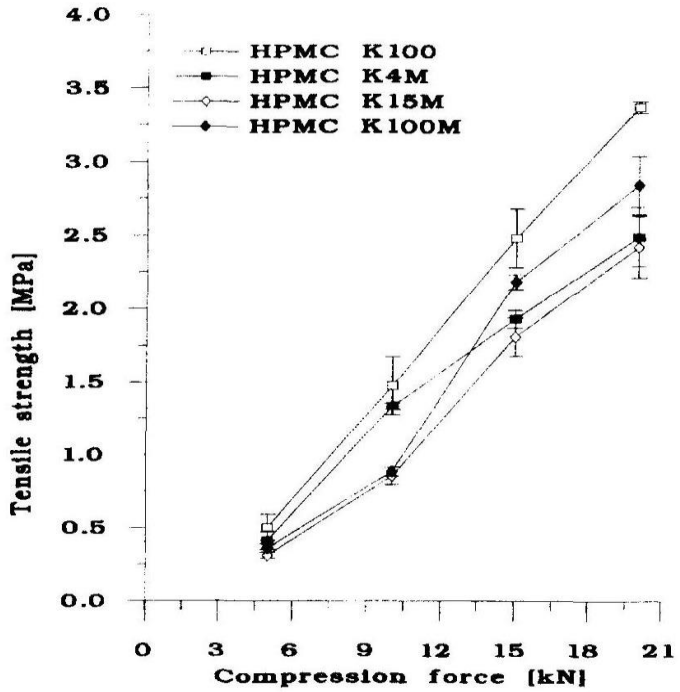


Figure 7. The influence of compression force on the tensile strengths of tablets compacted from different viscosity grades of HPMC (Nokhodchi et al. 1996 b)

4.3 Environmental variables

4.3.1 The role of temperature of production environment

The temperature of compacting environment and the instrument typically will typically increase during the compression process. Throughout scale up procedure, these changes

in the temperature may have significant impact on tabletability of materials (Cespi et al. 2013). Despite the possibilities to simulate, for example, the effect of rising compression speed using compaction simulators in a laboratory scale, imitating the rise of the of temperature during compaction is not possible during preformulation trials.

Cespi et al. (2013) have investigated the effect of the induced temperature during compaction where they have demonstrated the interrelation of temperature growth and tabletability of materials with different chemical and consolidating nature, namely microcrystalline cellulose (MCC), dicalcium phosphate dihydrate (PDC), ammonio methacrylate copolymer type B (EURC) and poly ethylene oxide 600,000 Da (PEO). Figure 8 displays that while PEO and EURC have shown a significant increase in tablet tensile strength, the tabletability profiles of MCC and PDC have not changed considerably due to rising temperature. It was explained by lower thermal transition temperatures of PEO and EURC that making them more sensitive to temperature fluctuations of production environment.

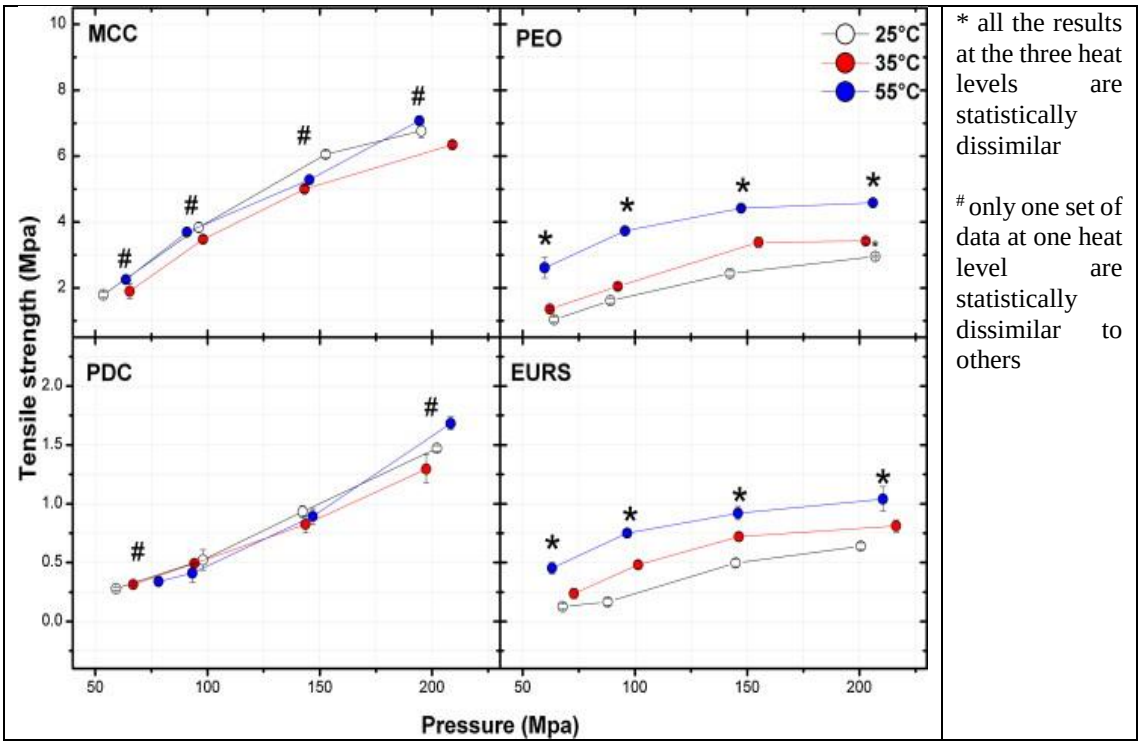


Figure 8. The tensile strength of tablets resulted from four different excipients during heat changes in tableting environment (Cespi et al. 2013)

The different work on this issue have also stated the dependency of compact's mechanical properties on temperature of manufacturing environment (Rouèche et al. 2006). During this study, the influence of a range of temperatures on compressional behaviour of organic materials was examined. Researchers have noted that organic materials, because of having lower melting point, are more prone to be affected by temperature escalations than minerals, exhibiting greater liquescing temperatures. The results suggested that the rise in temperature may increase the tabletability of organic materials until some point, in this case until 60°C. Further rise in temperature decreased the strength of tablets produced from these materials. The grow was explained by broader fragmentation that creating more interparticle contacts and hence expanding the strength of resulting compacts. However, heat over 60°C may cause formation of cracks in tablets during cooling after ejection, which lead to softening of compacts and decreasing of their strength.

4.3.2 The role of relative humidity of storage and production environment on determining the strength of tablets

Relative humidity (RH) of manufacturing environment also plays important role for determining the mechanical strength of compacts. It is true especially for materials which can absorb the free water in the atmosphere relatively fast. Sun (2008) has evidently demonstrated this effect by examining the effect of the RH levels of excipient storage environment on the tensile strength and other parameters of resulting tablets, such as porosity, plasticity and bonding strength. Researcher has noted that the moisture level contained in MCC powders, equilibrated in locations with various humidity levels, may vary significantly from one another. Moreover, the study reveals how quickly MCC can absorb the water from the atmosphere during the production, when stored in 0 or 11.6% humidity. Figure 9 shows the tensile strength values of tablets that were produced from various MCC lots, pre-stored in a range of RH levels, as a function of applied force. The figure clearly displays that the weakest tablets were obtained from the blend held in the environment maintaining highest RH. On the other hand, powders stored within 21.6% and 38.2% RH levels have produced strongest tablets. This was explained by formation of two water sorption layers, that increasing the hydrogen bonds. However extreme RH

levels may cause the more than two such layers. As a results, these layers start act like water thus weakening the potency of hydrogen bonds. Based on these results, it was recommended to keep the RH levels of production environment of MCC at the range 20% to 50% (Sun 2008).

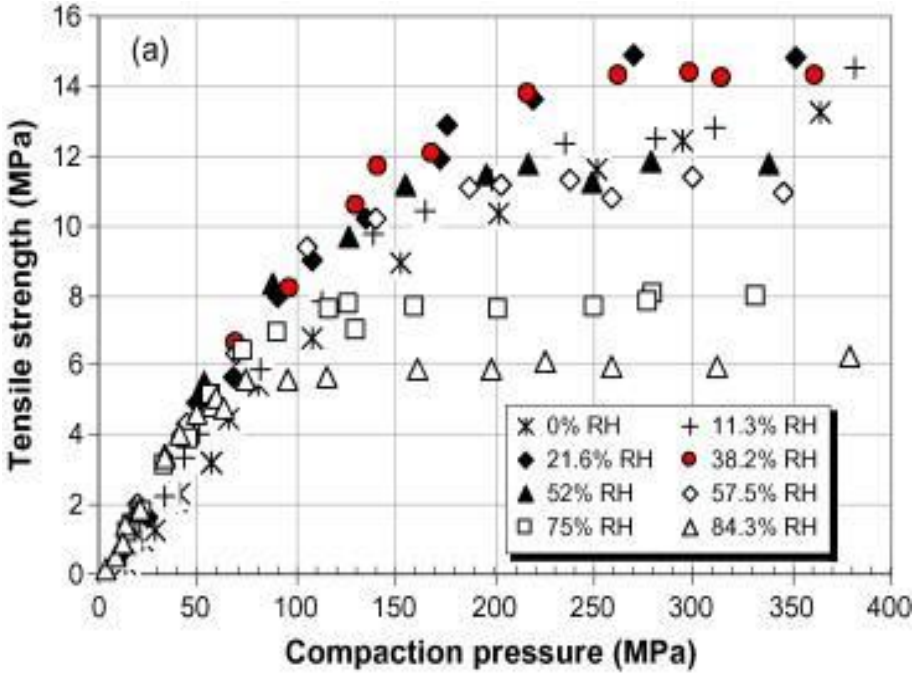


Figure 9. Tabletability of MCC powder butches equilibrated in various RH values (Sun 2008)

Ahlneck and Alderborn (1989) have investigated the effect of humidity of excipient storage environment on tensile strength of tablets made of six substances with varying consolidation features. They have clearly demonstrated that the absorbed water content of the powder, pre-stored in variety of RH levels, increase the tablet strength for most materials. However, all excipients reacted differently to the presence of additional water. With sodium chloride, sodium bicarbonate and saccharose, the maximum strength of tablets was obtained at medium RH levels and it decreased with rising humidity of storage conditions. In contrast, compacts produced from lactose and sodium citrate showed increasing strength throughout the whole RH growth. Moreover, acetylsalicylic acid exhibited very low sensitivity to increasing of moisture level, while the tabletability of Emcompress decreased only at high moisture levels. For increase of tensile strength

researchers have suggested two possible explanations. The first is the formation of solid bridges due to dissolution of surface molecules and crystallisation afterwards. The second is that the water molecules are integrated into the particles very well. Consequently, they act like a part of particles and improve their bonding capacity. On the other hand, decrease of tensile strength was explained by condensation of water on the particle surfaces due to high RH levels. This affected the mechanical properties of water soluble materials, like sodium chloride and saccharose, due to their liquefying.

5 AIMS OF THE STUDY

The main reason of this study was to examine the effect of speed increasing on the compressional behaviour of mixtures containing MCC and starch with various concentrations. MCC is known as a highly compressible excipient and starch shows very low compressibility – they well may be described as a two sides of extremity. Both of these excipients are very sensitive to lubrication. They consolidate by plastic deformation under compression. Since the plastic deformation is time dependent, it is justified to investigate the influence of tableting velocity on mechanical strength of compacts. The mechanical strength of the compacts was kept constant and only the force, that needed to get tablets with similar mechanical strength, has been adjusted during the increase of compaction speed. Thus, changes of applied force due to increasing tableting velocity was thoroughly investigated.

The next goal was the comparison of compaction behaviour of aforementioned ingredients during eccentric and rotary presses with respect to predictability these techniques from one another. Objective was also to find out the compaction speed and force limits, where the forming of coherent tablets is not anymore possible.

The third reason was to assess the effect of the lubrication on the mechanical strength of the resulting tablets. The effect of the lubrication on tablet properties has been studied only using eccentric machine. It can be considered that this effect will be similar in both machines.

Furthermore, tablet's porosity, elastic recovery and weight changes due to compaction speed variations were investigated. The influence of the additional tableting velocity and concentrations of each excipient on flow properties of powder blends was also examined.

6 MATERIALS AND METHODS

6.1 Materials

Excipients used in this experiment were microcrystalline cellulose, as an Avicel PH102 (FMC BioPolymer, Ireland), and maize starch, in the form of Hylon VII (National Starch & Chemical GmbH, Germany). 0,5 % MgSt (Magnesium Stearate Veg., Orion Pharma, Finland) was added to reduce sticking and support the ejection of compacts from the die. For the external lubrication 5 % m/m MgSt solution in acetone was used in some cases. Blending of powders was carried out in a Turbula shaker-mixer type T 2 A (Wily a. Bachofen, Switzerland). The weight of excipients was measured employing SG32001DR type scale (Mettler Toledo, Switzerland). Humidity of tableting environment was maintained by steam humidifier Condair MK5 Visual (Condair Ltd, Switzerland). Subsequently RH was tested with Mastech MS6900 moisture meter in the beginning of every tableting series. Water activity (a_w) of the formulation blends was measured using instrument AquaLab Series 3 TE (Dragon Devices, Inc. USA) just before the starting of each tableting process. Korsch EK O type (Korsch AG, Germany) (Figure 10A) single punch tablet press used for eccentric tableting. The rotational compaction was carried out by using Ronchi AM 13/8 (Ronchi, Italy) (Figure 10B).

A.

B.

Figure 10. Machines used in this experiment. A - Korsch EK O; B - Ronchi AM 13/8

The crushing strength of compacts was tested using hardness tester Schleuniger- 2E/205 (K. Schleuniger, Switzerland). Mettler AE 200 (Mettler Toledo, Switzerland) laboratory scale was used to determine the weight of tablets. The thickness and diameter of compacts were measured using the digital indicator SONY U30-F (Sony Magnescale Inc. Japan).

6.2 Methods

There were six different mixtures with various concentrations of MCC and Starch (Table 3). As it observable from the table, the mixture 1 and the mixture 6 have only one excipient excluding lubricant. Blends from 2 to 5 were produced by measuring first both excipients and then mixed in a turbula mixer for 10 minutes at speed 47 rpm utilizing glass container with about 50 % load. Resulted blend then mixed with the magnesium stearate for additional three minutes at the speed of 47 rpm. Concentration of the lubricant was 0,5 % and the amount of MgSt needed was calculated from a weight of the formulation mixture.

Table 3. Consistence of mixtures used in the experiment and planned tableting speeds for eccentric and rotary press

Mixtures	**Proportion of excipients**	**Speeds during eccentric press**	**Speeds during rotary press**
1	100 % MCC and 0 % Starch + 0,5 % MgSt	10, 20, 40, 60	17, 34, 51, 68
2	80 % MCC and 20 % Starch+ 0,5% MgSt	10, 20, 40, 60	17, 34, 51, 68
3	60 % MCC and 40 % Starch + 0,5 % MgSt	10, 20, 40, 60	17, 34, 51, 68
4	40 % MCC and 60 % Starch + 0,5 % MgSt	10, 20, 40, 60	17, 34, 51, 68
5	20% MCC and 80 % Starch + 0,5 % MgSt	10, 20, 40, 60	17, 34, 51, 68
6	0 % MCC and 100 % Starch + 0,5 % MgSt	10, 20, 40, 60	17, 34, 51, 68

To improve the effect of the lubricant-mixing, MgSt was put into the middle of the mixture to be lubricated. This was done by taking out the half of the powder from the container to another dish and then adding MgSt into the container. The half of the mixture, which was taken to the side, was then placed back to the container above MgSt. On the other hand, during preparation of the mixture containing the single excipient, the lubricant has been put into the middle of that excipient by the same way and mixed for three minutes at the speed of 47 rpm. The mixtures were prepared individually for each series of tableting, i.e. every mixture was prepared ahead of tableting and for one batch at time.

In the first stage of the tableting process, MCC was compacted without any other ingredient employing single punch tablet machine. The intention of this step was better understanding of its performance in the absence of other excipients. The next goal was to examine if any problems, such as sticking, will occur during compression of pure MCC. During this step, deepness of lower punch, which determines tablet's weight, was first 10 millimetres, then 8,5 millimetres and, at the end, 7 millimetres. Tablets were produced from all these lower punch positions using four different speed (Table 3). Set of 9 mm flat-faced plain punches were utilized and resulted tablets were round, flat-faced and without breaking line. Before starting of tableting at each speed, RH of tableting room and water activity of the mixture was measured using aforementioned equipment. Resulted tablets from each series then put into the brown bottles with the volume of 100 millilitres and they were researched about four hours after compaction. Tablets' weight, thickness, diameter and crushing strength were inspected.

Tensile strength of tablets was calculated from the crushing strength results according to equation (Fell and Newton 1970):

$$\boldsymbol{\sigma = \frac{2F}{\pi DH}} \qquad \text{(Eq. 2)}$$

where F is breaking force or crushing strength, D is diameter of tablet and H is the thickness of tablets.

Elasticity of the resulting tablets was also calculated, as this parameter can also be speed-dependent. Elastic recovery was calculated according to following equation (Adolfsson and Nyström 1996):

$$\boldsymbol{E_{\%} = \frac{T_{max} - T_{min}}{T_{min}} x100} \quad \text{(Eq. 3)}$$

where T_{max} is the tablets maximum thickness obtained during decompression, T_{min} is the tablets minimum achievable thickness.

Porosity of tablets was calculated according to following equation (Sun 2008):

$$\boldsymbol{\varepsilon = 1 - \frac{\rho_{tablet}}{\rho_{true}}} \quad \text{(Eq. 4)}$$

where ρ_{tablet} is a density of tablet and ρ_{true} indicates a true density of material. The density of tablet, on the other hand, can be calculated according to following equation:

$$\boldsymbol{\rho_{tablet} = \frac{M}{V} = \frac{M}{\pi r^2 h}} \quad \text{(Eq. 5)}$$

where M is the tablet's mass, V is its volume, r is radius and h is thickness.

In the next stage, mixtures containing various portions of MCC and starch with additional 0,5 % MgSt has been compressed at four speeds (Table 3). The punch set was as same as it was in the first stage. However, the deepness of the lower punch was constant at 8,5 mm during this stage. Before starting of tableting process, RH of tableting room and water activity of the mixture was measured using aforementioned equipment. Resulted tablets from each series then put into the brown bottles with the volume of 100 millilitres and they were researched about four hours after compaction. Tablet properties like weight, thickness, diameter and crushing strength were measured and tensile strength, density, and elasticity were calculated, in a same way as it described in the previous paragraphs.

In the last stage, mixtures were planned to press in the rotary tablet machine Ronchi series AM 13/8 with two punch pairs, at operating speeds were from 17 to 68 (Table 3). Punch type utilized during this stage was 9 mm flat-faced, bevel-edged and bisect. Shape of the resulted tablets was flat-faced, bevel-edged round tablets with a breaking line on one side. Resulted tablets from successful tableting series were investigated about four hours after the compaction. Tablet properties like weight, thickness, diameter and crushing strength were analysed with the methods which were mentioned in the previous paragraphs. The crushing strength values of tablets with the breaking line were not converted to the tensile strength values for the reason that the way tablets break can vary with these tablets (Podczeck et al. 2014). Additionally, researchers have noted that the position of breaking line does not significantly affect the amount of crushing strength values. However, they have recommended to keep angle of the breaking line constant to surface of platens, because dissimilar angles can cause variations of failure mechanism of these tablets. During testing of the crushing strength of scored tablets in this study, breaking line kept parallel with the platens' surface.

Elasticity profile of compacts resulted from rotational tableting has not been calculated. It was due to the lack of data needed to calculate the elasticity i.e. Ronchi AM 13/8, the machine used in this experiment, was not provided with the abilities for detecting the data about the upper and lower punches' positions.

The porosity and the density values were not calculated too for scored tablets. For the calculation of this parameters, it required first to calculate volume of the tablet. However, the volume calculation is very challenging in this case and it requires relatively complex equipment for its appropriate measurement.

7 RESULTS AND DISCUSSIONS

7.1 Eccentric press

7.1.1 Characterization of compaction process

Tabletability of pure MCC was very good and no any major challenges have occurred during lower speeds in eccentric press. Situation has changed dramatically with rising compaction velocity to 40 tablets per minute (tpm). Sticking was observed and ejection force was extremely high. Because of this issue, punch heads were treated with the MgSt solution just before tableting. This lubricant treatment of punch heads, also termed as an external lubrication, was decided to apply ahead of every tableting speed to prevent further sticking problems. External lubrication is believed to have insignificant effect on tablet mechanical properties comparing to internal lubrication (Yamamura et al. 2009).

During the compaction of mixtures 1 to 6 (Table 3), there were no any major issues have occurred. After having problems with sticking when no lubricant was added, it has been decided to add MgSt into all formulations. After using MgSt as a lubricant, no further problems with sticking of tablets to die wall or to punch surfaces were observed. It agrees with the statement of other study, where including MgSt into the formulation has completely eliminated the occurrence of those issues (Salpekar and Augsburger 1974).

However, the tensile strength values of pure starch tablets were not as it was planned, around 1.8 MPa. It was due to the limitations of applied force in the single press machine. Compression force values extremely high and the equipment alarmed due to it.

7.1.2 Weight changes

The position of lower punch was constant during compaction. First of all, the weight of tablets has grown independently from the consistence of formulation mixture by

additional tableting speed. It is observed for all mixtures: pure MCC, MCC with MgSt or MCC with starch and MgSt. It can be explained by the mechanism of die filling in this type of machines. At higher speeds, hopper moves quicker that improves powder flowability and, thus, the intensity of die filling improves. It can also be result of a breaking of cracks of the particles due to quick movement of shoe hopper, that facilitating the flow. Tablets were heavier, probably, as a result of these factors. One should take to account this property of eccentric tableting when different speeds are being compared. Figure 12 shows the changes in tablets' average weights observed during different lower punch positions: 7, 8.5 and 10 mm. In all cases tablets expressed minor increase in their mass.

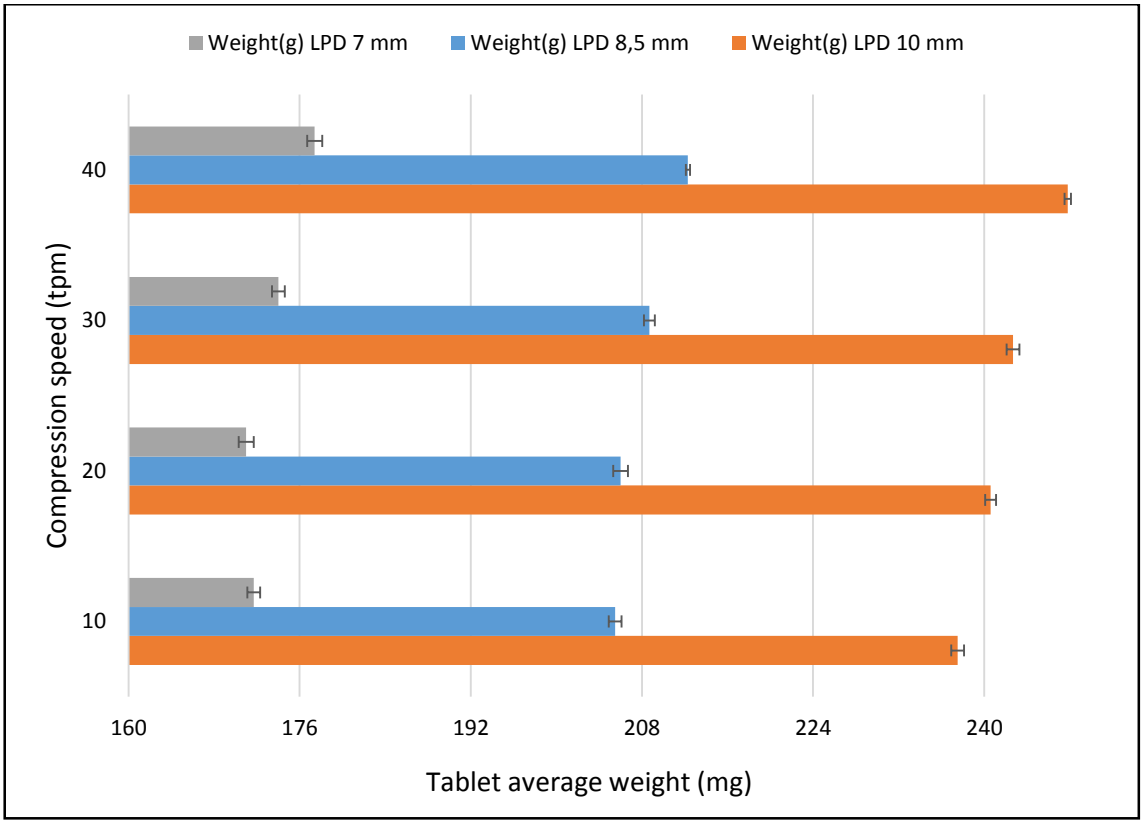
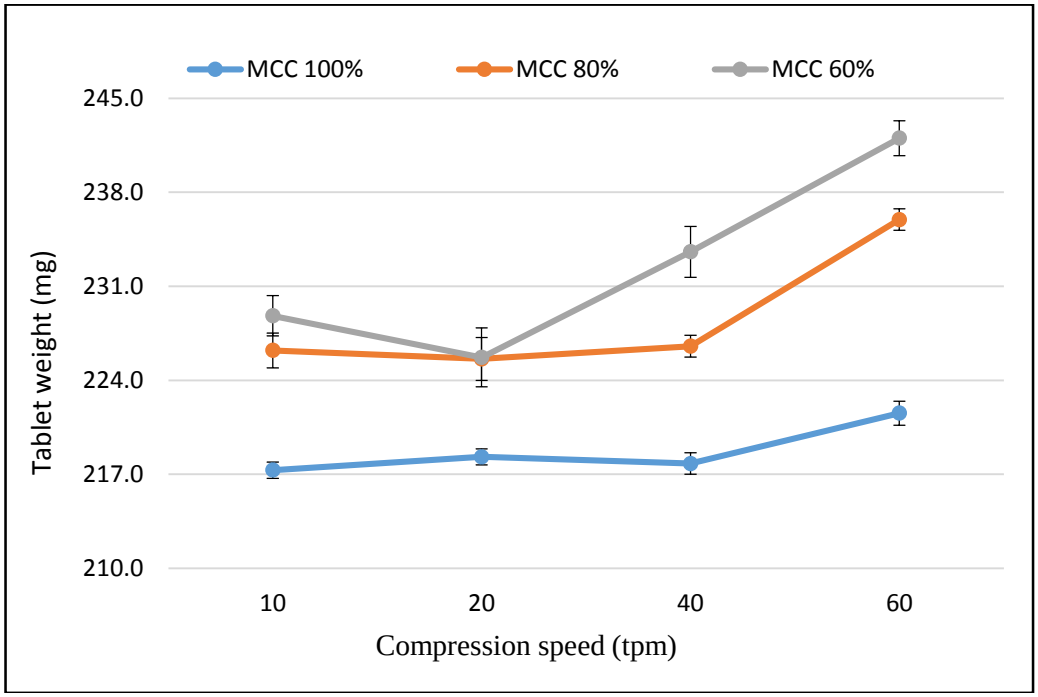


Figure 12. Changes of pure MCC tablets' average weights in various tabletting speeds and lower punch depths (LPD)

The weight changes during compaction of mixtures 1 – 6, described in the Table 3, are illustrated in the Figure 13. As it observable from the figure 13 A, the weight of MCC tablets were relatively stable during speed increasing.

A



B

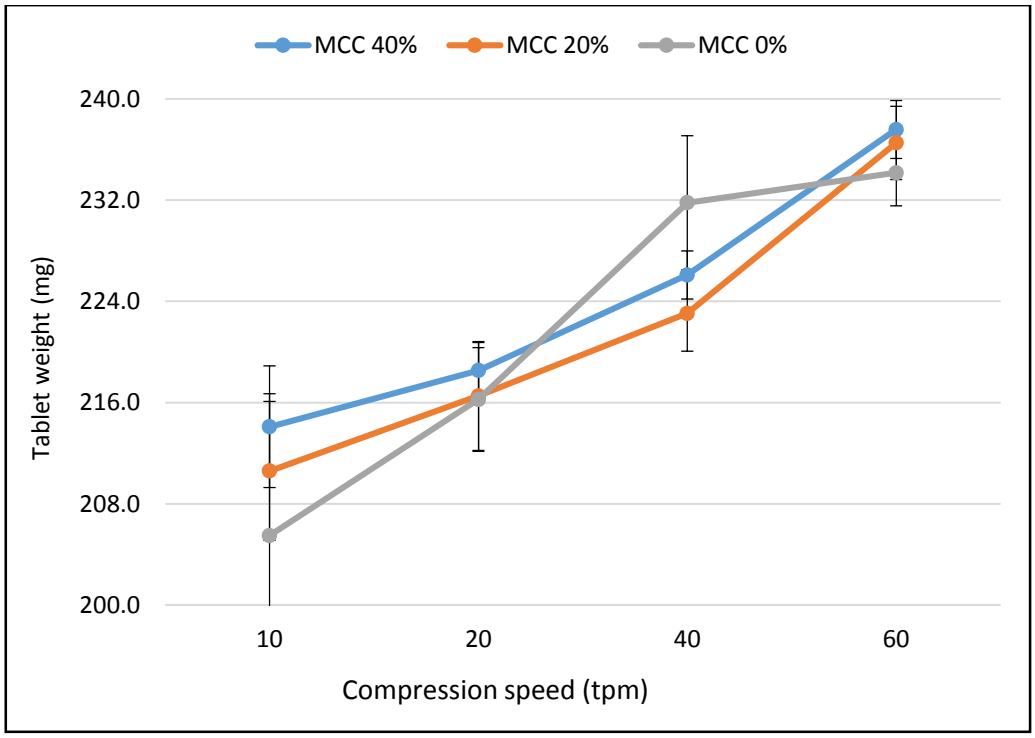


Figure 13. Changes of tablets' average weights in various tableting speeds. Tablets were resulted from compaction of blends with various portions of MCC: A – 100, 80, and 60%; B – 40, 20 and 0%

The tablets made of 80 and 60% MCC were relatively stable during lower speeds. However, their weight values have escalated in speeds above 20 tpm. On the other hand, the tablets produced from the last three mixtures, which contain 40, 20 and 0% MCC, have demonstrated extremely high increase in their mass with additional speed variations (Figure 13B). In some case, for example with 0% MCC, this increase was more than 15%. These results suggest that the starch tablets are more sensitive to speed variations than MCC tablets with respect to their weight.

7.1.3 Compression force changes

In the theoretical part of this study, the effect of the compression speed on the mechanical properties of final tablets were discussed quite comprehensively. Thus, this section will concentrate on analyses of obtained data. Figure 14 displays the force needed to get tablets with similar tensile strength as a function of punch velocity and excipient concentrations. Increasing of the tableting speed resulted the rising of the compression force needed to obtain tablets with the same strength.

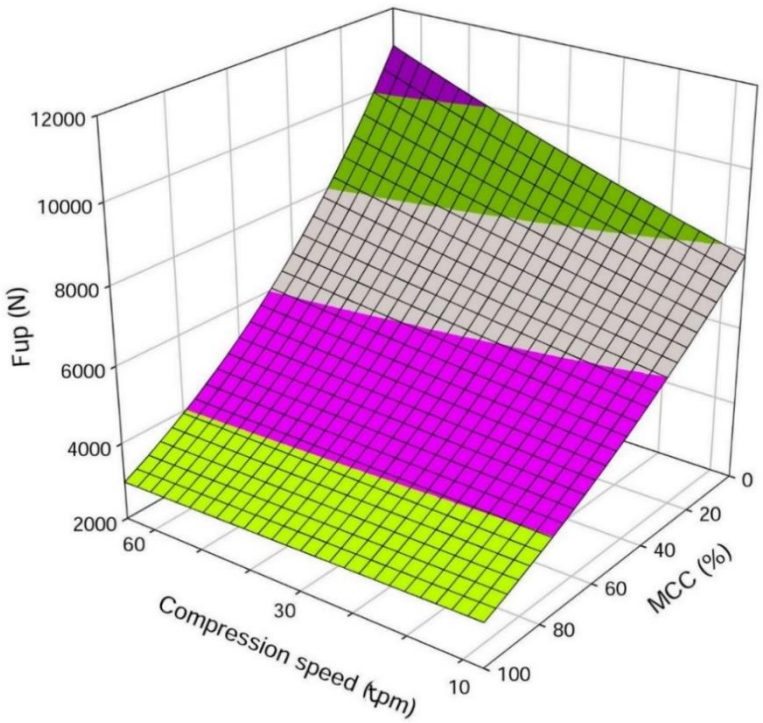


Figure 14**.** Upper punch force, needed to obtain tablets with similar tensile strength, as a function of compression speed and the excipient concentrations

With falling of MCC concentration in the formulation from initial 100 % to 0 %, almost fourfold force needed to obtain tablets with similar tensile strength. Pure MCC has reacted to the speed variation very smoothly. The force changes were insignificant in this case. When the concentration of starch reached 40%, the mixture has started to be more sensitive to speed variation. As a result, higher speeds required larger compression force values in this case. The most considerable force changes, due to additional speeds, was observed during compaction of the pure starch.

7.1.4 Elastic recovery changes

It is believed that the elastic recovery, also called as an elastic relaxation, is caused by the energy cumulated inside the pressed material (Haware et al. 2010). The elastic recovery was calculated directly from the operational data, which shows the positions of upper and lower punches during compression, and the thickness of the tablets by the aforementioned equation (Eq. 3). Then the results of elastic recovery were compared with the compression speed and the concentration of two excipients.

Figure 14 shows elasticity profiles of compacts pressed using eccentric machine as a function of compression speed and MCC-starch concentrations. As it can be clearly seen from the figure, rising compression speed was definitely influenced the elastic recovery of compacts. With the additional speed, in all cases, elasticity has been increased. On the other hand, higher concentration of starch has caused greater elastic recovery. However, during lower concentrations of starch, the elastic recovery changes between tableting series of the same mixture was more significant.

As it described in earlier studies, more elastic recovery leads to weaker tablets, which is a result of decline in an interparticle bonding (Haware et al. 2010; Adolfsson and Nyström 1996). These works also showed that the excess energy during compression expands the elastic recovery. In this study, as compression force increased by additional starch in the formulation, this excess force has probably played very important role in increasing the elastic recovery of compacts.

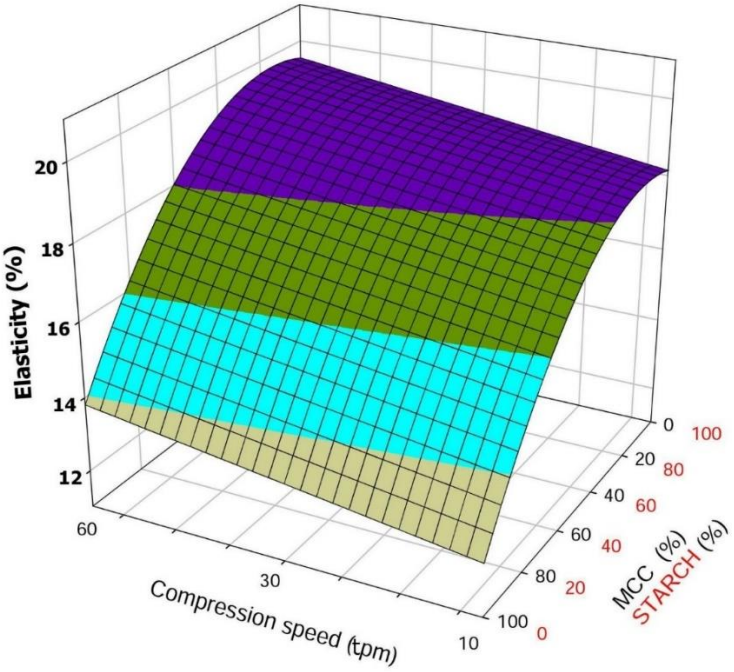


Figure 15. Elasticity of compacts resulted from eccentric press as a function of compression speed and excipient concentration in the mixtures.

7.1.5 Porosity changes

As tablet can be described as an air phase spread in a continuous solid phase (Nyström et al. 1993), it contains interior air voids (Paronen and Ilkka 1996). These air voids exist between particles or inside them. The term porosity describes all pore space in powder column, both intra- and interparticulate air phases. In general, porosity decreases with increasing compression force. It's the result of a removal of air voids between particle during volume reduction. The next porosity reduction take place when the solid particles start to deform or to fragment. This, in turn, decreases the pore spaces inside particles.

In this work, the porosity values of tablets have displayed dissimilar tendencies. First, the porosity of MCC tablets was more stable during speed increases and only slightly decreased during speed addition from 40 to 60 tpm. Second, additional starch concentration in the formulation always meant less initial porosity. Moreover, tablets produced from these formulations have demonstrated higher sensitivity to speed

increasing, compared with tablets pressed from blends with less starch. The blend containing 20% starch has displayed almost similar trend to pure MCC tablets (Figure 16). With more starch, the porosity has decreased considerably during speed expansions. The decreasing occurs, probably, due to the increasing of applied force, which is needed to obtain tablets with similar strength, as this increasing was more significant in cases where starch concentrations were 60, 80, and 100% in the formulations (Appendix 2).

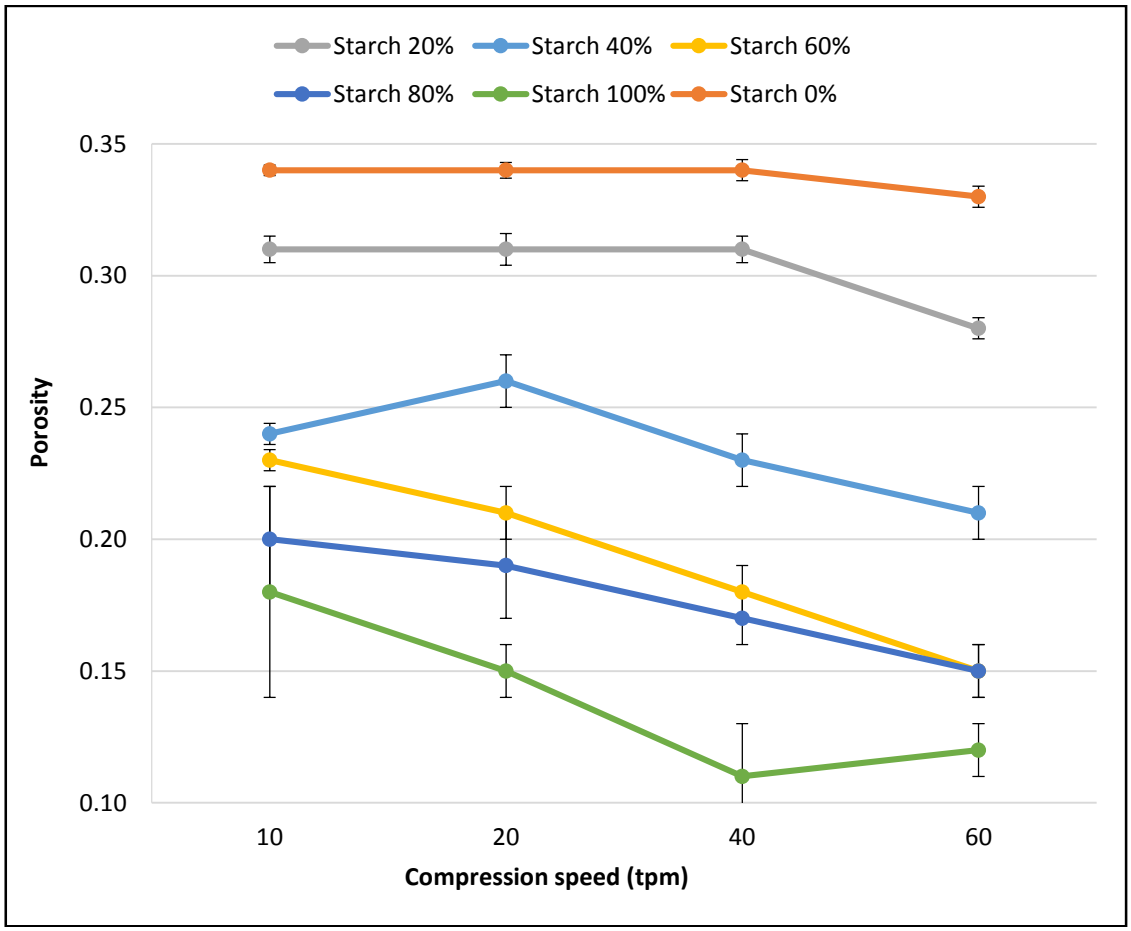


Figure 16. Porosity changes of tablets compressed from blends, with variety of proportion of starch, as function of compaction speed

7.1.6 Density changes

Densification of powder bed under the applied force is believed to be very important step during compaction process (Fell and Newton 1971). Density of tablet shows its mass as

a function of volume. Contrary to the porosity, it rises when additional force is applied. Density value of tablets, which were produced from the blends 1 – 6, showed opposites of porosity values. The lowest density values were expressed by tablets produced from MCC powders without starch (Figure 17). Whereas densest tablets were obtained during the compaction of starch powders. Tablets pressed from MCC were also the most stable during speed increasing. Situation has changed when concentration of starch reached 40% in the formulation. After that limit, all blends have demonstrated the increase of tablet density with additional tableting velocity. On the hand, there has been observed decrease of density during speed rise from 40 to 60 tpm with respect to 100% starch formulation.

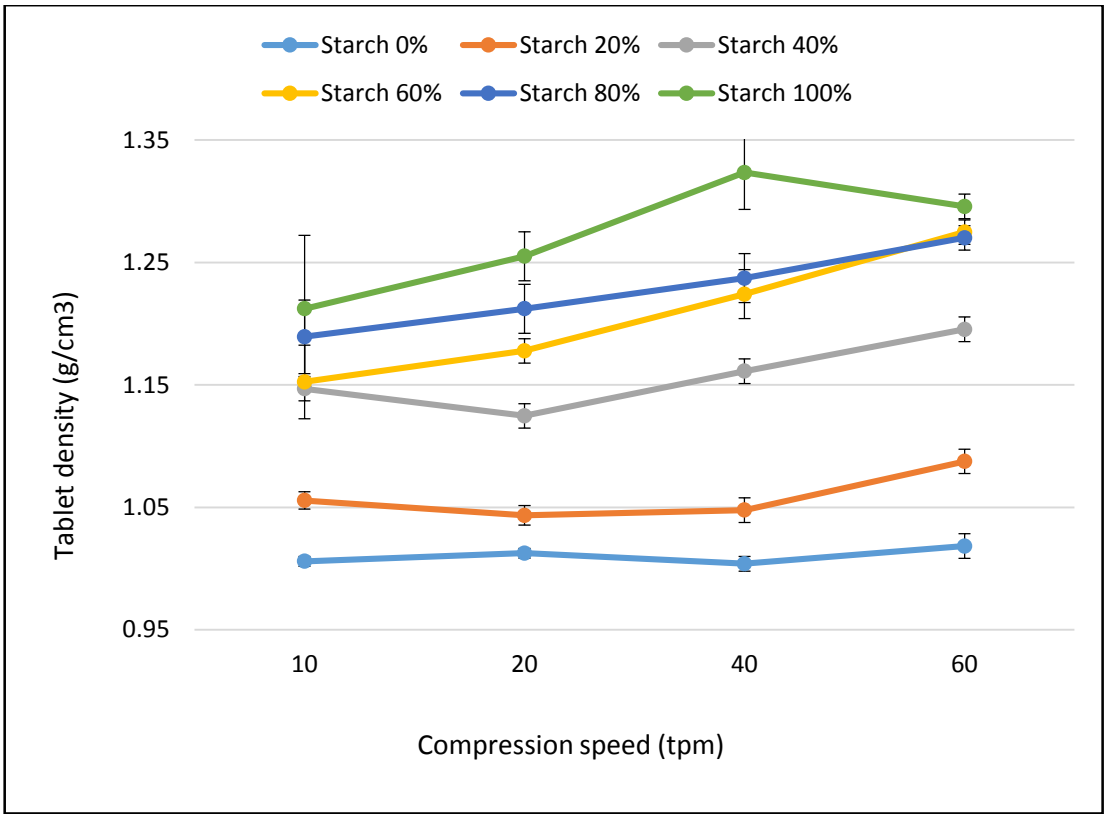


Figure 17. The density changes of tablets, made of various formulations, as function of compression speed

7.1.7 Effect of the MgSt on compaction parameters

7.1.7.1 Weight changes

Magnesium stearate is used mostly as a lubricant. It expresses also some flowability improving abilities, i.e. glidant properties, and often used as a flow enhancer (Li and Wu 2014). Its glidant properties can be explained by its ability to cover the surface of particles hence reducing their sticking to each other (Wang et al. 2010). It can reduce the interparticle attractions between particles as well (Li and Wu 2014). In this study, formulations with this lubricant has shown better flowability compared to the formulations without lubricant. It can be understood by analysing the tablets' weight changes, as this value depends on amount of powder flown into the die.

The weight of tablets, resulted from lubricated mixture, was significantly higher than those made of unlubricated ones (Figure 18). They were also relatively stable until the speed of 40 tpm, but slightly increased after that. The weight of the pure MCC tablets was more sensitive to speed increases, as they showed gradual weight increasing due to higher speeds. However, the rise was more noteworthy during speeds between 20 – 60 tpm.

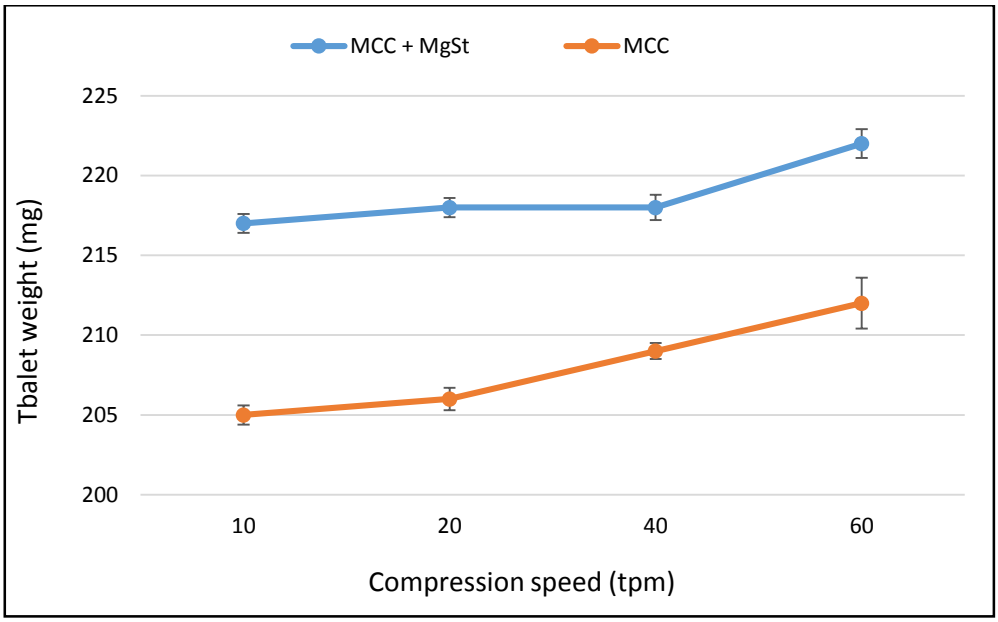


Figure 18. Changes of tablets' average weights, compacted from blends with and without MgSt, during the speed increasing

7.1.7.2 Ejection force changes

Boundary lubricants, such as MgSt, are able to reduce the shear stress inside the die, which in turn reduces the ejection force value (Li and Wu 2014). As it observable from the Figure 19, inclusion of MgSt into the formulation has dramatically decreased ejection force values. In the lowest speeds, this decrease was more than three times. Additionally, in cases with lubricant, ejection force was more stable at higher speeds compared to the cases where there was no lubricant used.

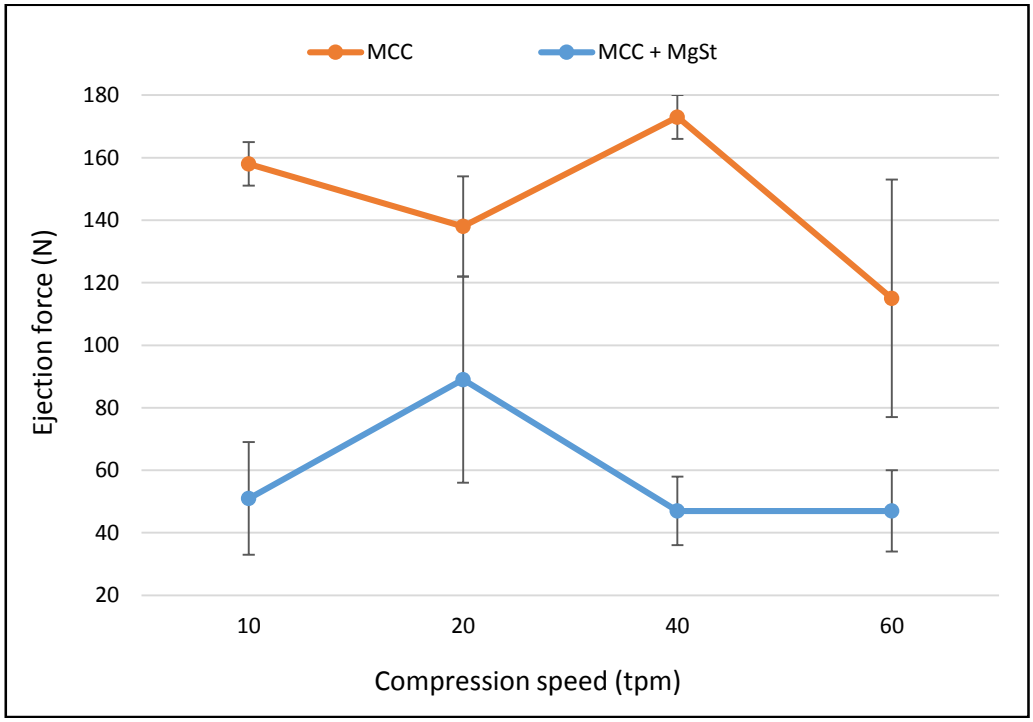


Figure 19. Ejection force – compression speed profiles for tablets compacted from blends with and without MgSt

7.1.7.3 Porosity changes

The porosity of tablets, with or without lubricant, responded with a different way to the speed increasing. Lubricated tablets showed porosity increase at speeds 40 and 60 tpm and were constant at lower speeds. In contrast, the tablets without lubricant expressed no

change in their porosity values up to 40 tpm (Figure 20). They showed slight decrease with adding the tableting speed from 40 to 60 tpm.

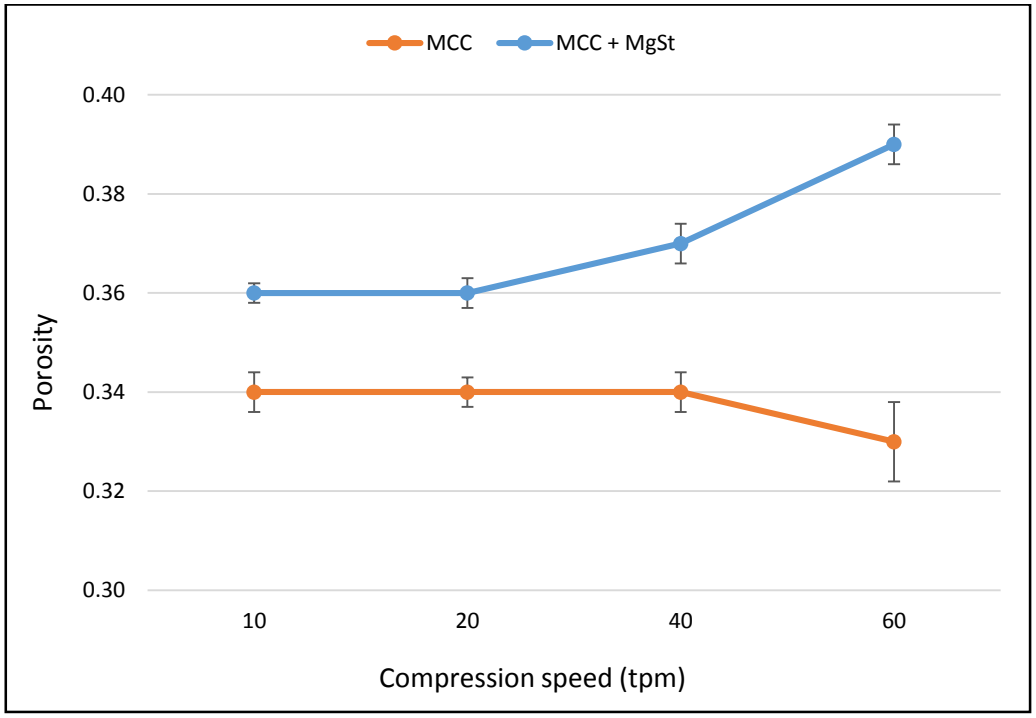


Figure 20. Porosity - compaction speed profile for tablets compacted from blends with and without MgSt

The dependency of porosity on applied force was discussed in the section 7.1.5 and, as it understood, less porous tablets may be produced by higher pressures. In this study, lubricated tablets required less pressure to get tablets with similar strength compared to unlubricated ones. This occurrence can be explained by increased tablet weight, due to which the applied force was smaller. The cause of tablet weight increases, by addition of MgSt, was discussed in the section 7.1.7.1

7.2 Rotary press

7.2.1 Characterization of compaction process

Probably the most noteworthy problem with the rotary press was flowing of the mixture onto very short area, which is why die filling was not appropriate. Furthermore,

mechanism designed for vibrating or shaking the hopper to facilitate the flow area was not able to improve it. This problem was solved with additional movement of hopper by the operator during compaction, aiming support of a flow and expand the die filling area. Hopper was also moved to a higher position by adjustment screws.

Although the compression mostly succeeded with the formulations containing lower concentrations of starch in rotary press, challenges started to occur when the portion of starch reached 60 %. During compression of those mixtures, it was impossible to get tablets maintaining their physical integrity at the speed of 51 rpm and above. Tablets' sizes were fluctuated significantly in addition to tablet weight deviation. Mixtures 5 and 6, containing 80 and 100 % of starch respectively, have not been successfully compacted employing the rotary machine at any tableting speed, regardless of their acceptable performance during the eccentric press (Figure 21).

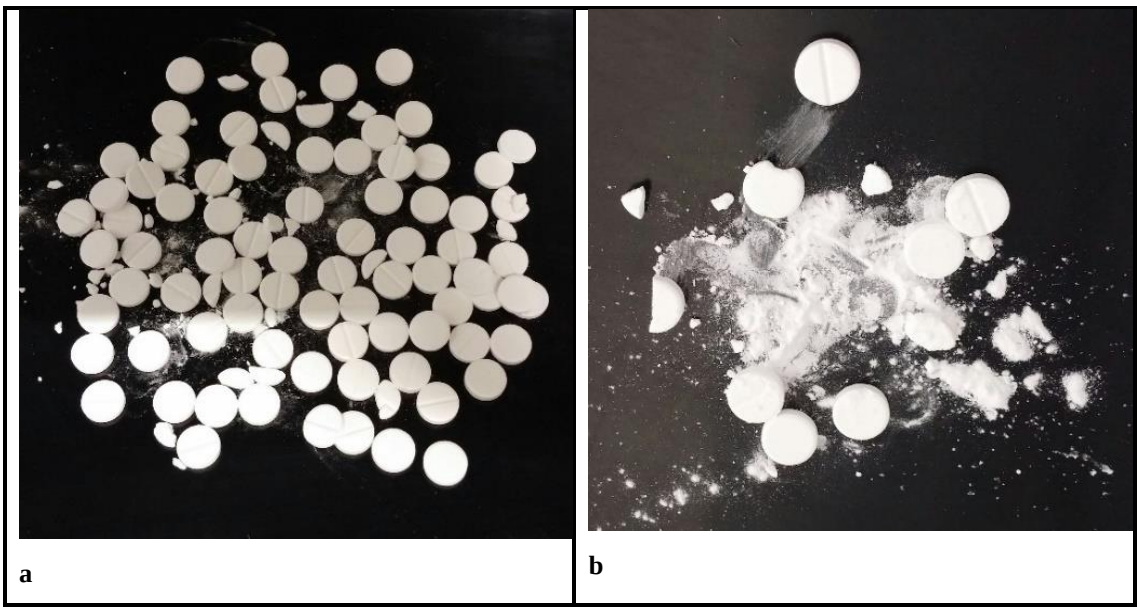


Figure 21. Resulted tablets during rotational press of the formulation containing 80% (a) and 100% (b) of starch

Blend containing 80 % of starch resulted dissimilar tablets and broken tablets (Figure 21a). With 100% starch, tableting was impossible due to the very weak die filling, which leaded to unformed half-tablets or, even worse, there have been only powder coming out from the machine Figure 21b.

7.2.2 Weight changes

Results obtained from rotational press were significantly different from eccentric press regarding to weight changes. The average weight of the tablets has decreased with additional tableting speed during the all successful tableting series (Figure 22). This can be explained by the mechanism of die filling in the rotational tablet machines. Flowing of the mixture into the die is affected by the speed of turret, because there is a less time available for filling of the die, compared to lower speeds. The decreasing of tablet weight was more significant in case where 100 % MCC was compacted. Additional starch has reduced the intensity of weight decrease. The decrease was less sharp with rising concentrations of starch. In contrast, the blend containing 80% MCC and 20% starch showed the most stable trend

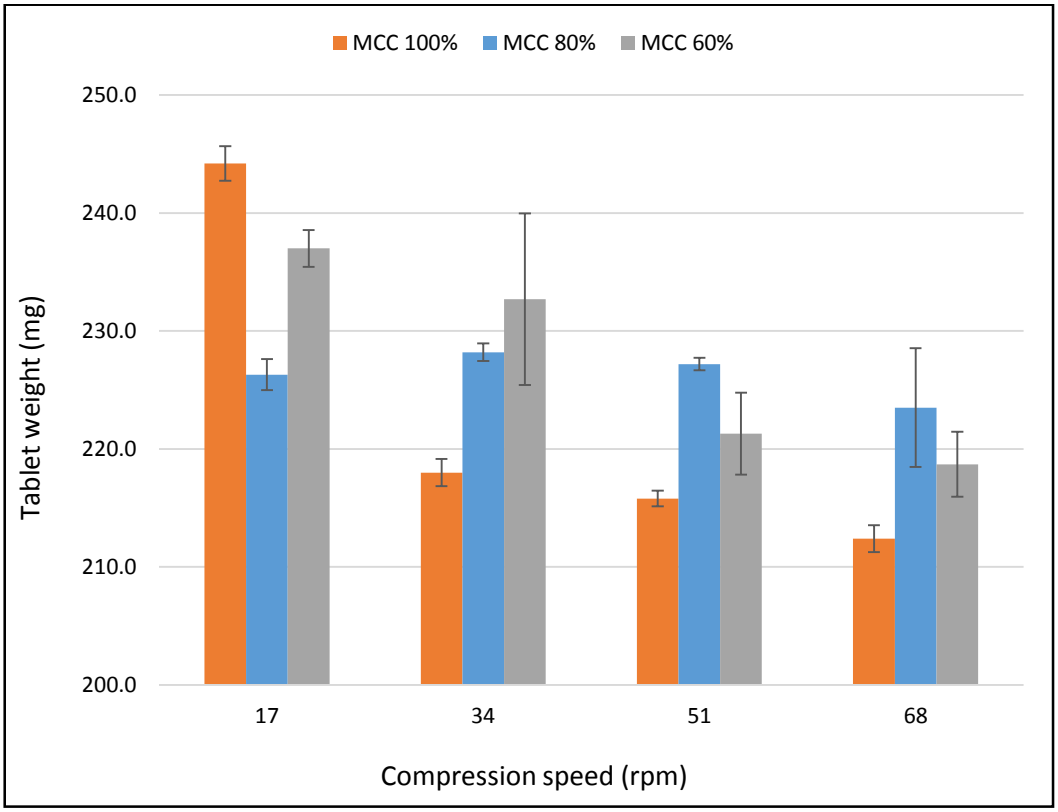


Figure 22. The tablets' average weight changes due to the increasing compaction velocity during rotational press

7.2.3 Compression force changes

The relation between compression force and speed was similar to the results of the eccentric press. With additional tableting velocity, more compression force was needed to produce tablets with the similar crushing strength (Figure 23). However, the alterations of applied force were less significant compared to the eccentric press. As it can be seen from the figure, additional speed has increased the compression force in all cases. This increase was more considerable in cases where starch concentration was more than 40 %.

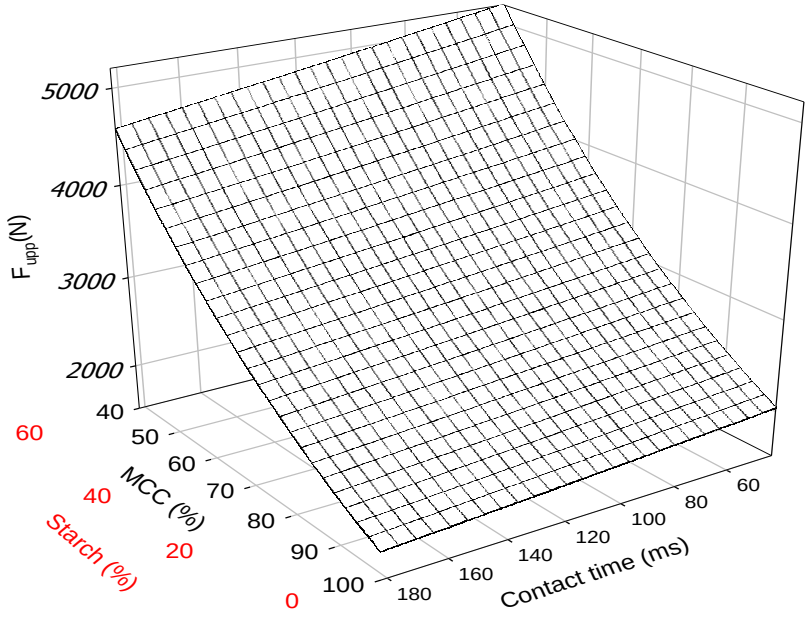


Figure 23**.** Upper punch force, needed to obtain tablets with similar crushing strength, as a function of compression speed and the excipient concentrations

8 CONCLUSIONS

In terms of compression force, it has displayed the increase with the rising compaction velocity, during both the eccentric and rotary presses. It can be concluded that if the force had been constant throughout the compaction process, then the strength of tablets would have been decreased in all cases, due to the increasing of tableting speed. It agrees with the results of previous works, where plastic materials, as was in this work, have demonstrated time-dependency regarding to the strength of tablets made of these materials (Ruegger and Çelick 2000; Ishino et al. 1990; Tye et al. 2005).

Speed-dependency of tablet properties, such as porosity and density, was also successfully shown using the eccentric press. During this process, the porosity of tablets has decreased with additional compression speed. On the contrary, the density values have shown an increase. These occurrences may be explained by the relations between compression force and those parameters. More compression force reduces the air voids, between the particles and inside them, more effectively and, as a result, tablets are less porous (Paronen and Ilkka 1996). This, in turn, rises the density of tablets. More density values mean greater tablet mass in a defined volume.

The elastic recovery values have increased with the additional speed in all cases during the eccentric press. Higher concentration of starch has resulted greater elastic recovery. It can be concluded that the starch exhibits more elastic behaviour than MCC.

With respect to predictability of these tableting methods from each other, it can be concluded that both methods require more compression force, which is needed to obtain tablets with similar strength, with additional tableting velocity. Regarding to tablets' weight changes, throughout the increasing of the tableting speed, they have demonstrated opposite trends. Increase of tablets' weight was observed during the eccentric press and its decrease was observed during the rotary press respectively. It can be explained by their different die-filling process. Other important parameters, such as elastic recovery, the porosity and the density, were not calculated regarding to the rotary press, because of the

complexity of volume calculation of scored tablets. It made impossible to compare these methods with respect to those parameters.

In this thesis, the tensile strength, during the eccentric press, and the crushing strength, during rotary press, was planned to keep in pre-determined limit by adjusting the compaction force values. However, it was not always possible to get very similar tablets regarding to their mechanical strength, mainly because of the differences of die filling, which in turn was very sensitive to the speed and to the concentrations of the excipients in the formulation. Less MCC and more starch in the formulation indicated poorer flowability, leading to variations in the die filling. Additionally, there were compression force limits in the settings of machines, over which compression would be less appropriate. Moreover, the tensile strength of tablets was not calculated for the scored tablets, which were produced during rotary press, and the compression force was adjusted according to the crushing strength values. The reason for that was the fracture variations of such tablets during diametrical compression, due to which it was advised not to convert their crushing strength values to the tensile strength values (Podczeck 20104). The comparison of these tableting methods, eccentric and rotary, would have been more appropriate if the resulted tablets from both methods were similarly scored or unscored. This, in turn, would give the possibility of comparing them according to the similar strength values of resulted tablets.

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APPENDICES

Appendix 1. Results obtained from eccentric press

Mixtures	Compaction speed, tpm	Weight, g	Thickness, mm	Diameter, mm	Crushing Strength, N	Tensile strength, MPa	Density, g/cm3	Porosity	Contact time, mc
1	10	217±0,6	3,38±0,01	9,02±0,01	83±1,8	1,73±0,03	1,01±0,004	0,34±0,002	1646
	20	218±0,6	3,38±0,01	9,01±0,004	81,2±2,1	1,70±0,04	1,01±0,004	0,34±0,003	864
	40	218±0,8	3,40±0,01	9,01±0,005	81,3±1,2	1,69±0,03	1,00±0,01	0,34±0,004	455
	60	222±0,9	3,41±0,01	9,01±0,004	83,9±2,0	1,74±0,04	1,02±0,01	0,33±0,004	287
2	10	226±1,3	3,36±0,01	9,02±0,006	74,8±3,8	1,57±0,1	1,06±0,01	0,31±0,004	1656
	20	226±1,6	3,39±0,02	9,01±0,005	69,5±2,4	1,45±0,1	1,04±0,01	0,31±0,01	841
	40	227±0,8	3,39±0,02	9,02±0,01	71±2,8	1,48±0,1	1,05±0,01	0,01±0,005	446
	60	236±0,7	3,40±0,02	9,01±0,003	86,6±2,1	1,80±0,04	1,09±0,01	0,28±0,004	281
3	10	229±1,5	3,12±0,01	9,02±0,01	82,5±3,7	1,86±0,1	1,15±0,01	0,24±0,004	1672
	20	226±2,2	3,14±0,03	9,02±0,005	76,8±7,1	1,73±0,2	1,12±0,01	0,26±0,01	834
	40	234±1,8	3,15±0,02	9,02±0,004	88,3±5,1	1,98±0,1	1,16±0,01	0,23±0,01	453
	60	242±1,3	3,17±0,02	9,01±0,001	101,5±5,3	2,26±0,1	1,20±0,01	0,21±0,005	286
4	10	214±4,8	2,91±0,01	9,01±0,01	62,9±7,9	1,53±0,2	1,15±0,03	0,23±0,02	1672
	20	219±2,2	2,91±0,02	9,00±0,003	68,5±4,4	1,66±0,1	1,18±0,01	0,21±0,01	841
	40	226±1,8	2,91±0,02	8,99±0,004	82,8±7,6	2,02±0,2	1,22±0,02	0,18±0,01	444
	60	238±2,3	2,93±0,01	8,99±0,005	99,8±7,5	2,41±0,2	1,27±0,01	0,15±0,01	286
5	10	211±5,5	2,78±0,02	9,01±0,01	56,7±7,3	1,44±0,2	1,19±0,03	0,20±0,02	1641
	20	217±4,3	2,80±0,02	9,01±0,01	59,3±7,5	1,50±0,2	1,21±0,02	0,19±0,02	854
	40	223±3,0	2,83±0,01	8,99±0,01	61,6±3,6	1,54±0,1	1,24±0,02	0,17±0,01	463
	60	237±2,9	2,93±0,02	8,99±0,01	76,1±3,9	1,84±0,1	1,27±0,01	0,15±0,01	289
6	10	206±11,2	2,65±0,03	9,02±0,02	47,5±15,4	1,26±0,4	1,21±0,06	0,18±0,04	1666
	20	216±4,1	2,70±0,02	9,01±0,01	54,2±13,9	1,42±0,02	1,26±0,02	0,15±0,01	845
	40	232±5,3	2,75±0,03	9,00±0,01	37,6±13,2	0,96±0,3	1,32±0,03	0,11±0,02	449
	60	234±2,6	2,84±0,02	9,00±0,003	39,5±14,3	0,98±0,4	1,30±0,01	0,12±0,01	290

Appendix 2. Results obtained from eccentric press

Mixtures	Compaction speed	Upper compression force (N)	Lower compression force (N)	Ejection Force, N	Upper punch displacement (mm)	Lower punch displacement (mm)	Minimum Thickness (mm)	Elastic recovery (%)	Water activity
1	10	3068	2159±29	51±18	5,55	8,58	3,03	11,8	0,252
	20	3122	2205±50	89±33	5,57	8,59	3,02	12,0	0,255
	40	3003	2103±29	47±11	5,55	8,58	3,03	12,4	0,259
	60	3032	2102±46	47±13	5,59	8,57	2,97	14,7	0,275
2	10	3794	2626±62	46±12	5,67	8,58	2,92	15,2	0,295
	20	3685	2536±65	46±14	5,65	8,58	2,93	15,7	0,301
	40	3640	2480±55	42±15	5,66	8,57	2,91	16,3	0,303
	60	3886	2697±37	43±12	5,65	8,58	2,93	16,3	0,298
3	10	5051	3777±117	52±12	5,93	8,60	2,67	17,2	0,286
	20	4912	3644±155	52±14	5,92	8,60	2,68	17,4	0,288
	40	5372	3987±132	53±15	5,92	8,59	2,67	18,1	0,290
	60	5692	4277±99	49±13	5,92	8,59	2,67	18,8	0,290
4	10	5654	4247±309	40±11	6,11	8,60	2,49	16,9	0,264
	20	6013	4534±300	40±13	6,08	8,60	2,52	15,7	0,236
	40	6796	5239±262	43±13	6,16	8,60	2,44	19,1	0,273
	60	7744	6123±268	43±10	6,15	8,60	2,45	19,6	0,265
5	10	6526	5035±711	39±14	6,27	8,61	2,34	18,9	0,250
	20	7562	5945±436	44±13	6,27	8,61	2,34	19,7	0,241
	40	7871	6205±374	43±11	6,27	8,61	2,34	21,1	0,242
	60	8491	6790±449	42±13	6,13	8,60	2,47	18,4	0,252
6	10	8254	6718±1262	42±13	6,40	8,62	2,22	19,3	0,235
	20	9912	8185±997	46±13	6,39	8,63	2,24	20,8	0,233
	40	10734	8943±892	42±14	6,34	8,63	2,29	20,1	0,249
	60	12598	10741±770	36±11	6,30	8,63	2,33	21,7	0,256

Appendix 3. Results obtained from rotary press

Mixtures	Compaction speed, rpm	Weight, g	Thickness, mm	Diameter, mm	Crushing strength, N
1	17	244±0,001	3,85±0,01	9,00±0,01	89,80±2,39
	34	0,218±0,001	3,36±0,01	9,00±0,00	85,80±2,53
	51	0,216±0,001	3,39±0,01	9,01±0,00	83,40±0,84
	68	0,212±0,001	3,31±0,02	9,01±0,00	86,30±2,00
2	17	0,226±0,001	3,29±0,01	8,99±0,01	90,30±2,87
	34	0,228±0,001	3,30±0,01	8,99±0,01	88,00±2,26
	51	0,227±0,001	3,37±0,02	9,00±0,00	79,40±1,78
	68	0,224±0,005	3,21±0,01	9,00±0,01	86,50±8,32
3	17	0,237±0,002	3,31±0,01	9,00±0,01	83,90±3,38
	34	0,233±0,007	3,18±0,02	9,00±0,00	87,60±10,66
	51	0,221±0,003	3,08±0,02	9,00±0,00	81,30±6,13
	68	0,219±0,003	3,06±0,01	9,00±0,00	78,10±5,26
4	17	0,225±0,008	2,88±0,04	8,99±0,01	93,60±9,38
	34	0,229±0,040	2,96±0,19	8,99±0,03	100±65,12

Appendix 4. Results obtained from rotary press

Upper compaction force (N)	Lower compaction force (N)	Upper punch contact time (ms)	Lower punch contact time (ms)	Water activity
1829±55	1749±60	188	191	0,307
1954±109	1919±106	91	93	0,301
1846±39	1762±48	60	60	0,273
1930±48	1877±62	45	45	0,299
2395±79	2551±84	174	181	0,269
2559±54	2679±69	95	99	0,279
2456±50	2563±58	58	60	0,273
2723±310	2856±293	42	43	0,270
3188±139	3205±160	171	177	0,264
3555±272	3604±287	86	89	0,251
3502±251	3521±250	57	59	0,246
3357±130	3358±131	43	44	0,244
4842±531	5050±557	169	174	0,262
5589±3218	5805±3345	84	87	0,251